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(71) Applicant : **NEUROSEARCH A/S**
Smedeland 26B
DK-2600 Glostrup (DK)

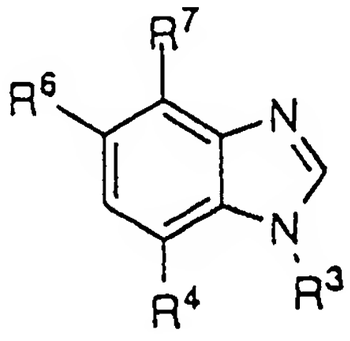
(71) Applicant : **MEIJI SEIKA KAISHA LTD.**
4-16 Kyobashi 2-chome
Chuo-ku Tokyo 104 (JP)

(72) Inventor : **Axelsson, Oskar**
Stora Kvarngatan 5-604
S-211 27 Malmö (SE)
Inventor : **Teuber, Lene**
Anemonevej 32
DK-3500 Vaerlose (DK)
Inventor : **Wätjen, Frank**
Afaldet 22
DK-2730 Herlev (DK)

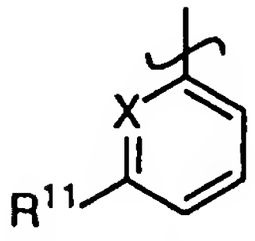
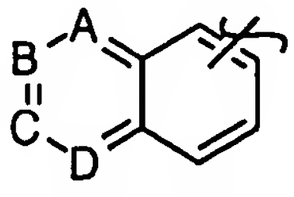
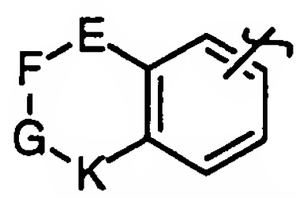
(74) Representative : **Wulff, Peter Samuel**
c/o NeuroSearch A/S,
Smedeland 26B
DK-2600 Glostrup (DK)

(54) Benzimidazole useful in the treatment of central nervous system disorders.

(57) Compounds having the formula :



or a pharmaceutically acceptable salt thereof
wherein
R^3 is

 ,  or 

are useful for the treatment of various central nervous system disorders such as epilepsy and other convulsive disorders, anxiety, sleep disorders and memory disorders.

EP 0 616 807 A1

This invention relates to novel benzimidazole compounds, pharmaceutical compositions thereof, a method of treating therewith, and to a method of preparing such benzimidazole compounds. The novel compounds are useful in the treatment of central nervous system diseases and disorders, and for example in the treatment of convulsions, anxiety, sleep disorders, and memory disorders.

Background of the invention

It is a well known fact, that specific sites in the central nervous system (the CNS) of a living animal body, including a human, exhibit highly specific binding for benzodiazepines such as for example diazepam. These binding sites are named benzodiazepine receptors. Lately, several subtypes of such benzodiazepine receptors have been isolated and described by techniques of modern molecular biology.

Numerous compounds belonging to different series of compounds having affinity for the benzodiazepine receptors have been synthesized during the last three decades. However, although the benzodiazepine receptor sites still are considered as very attractive biological sites for interfering with the CNS to treat various disorders and diseases, then nearly all previously synthesized compounds acting at these receptor sites have failed during clinical development because of unacceptable side effects.

Therefore, there is still a large need to identify novel compounds interacting with the benzodiazepine receptors.

Object of the invention

It is an object of the present invention to provide novel benzimidazole compounds and pharmaceutically-acceptable acid addition salts thereof, which are useful for the treatment of central nervous system disorders, diseases or ailments, and especially for the treatment of convulsions, anxiety, sleep disorders, and memory disorders.

Another object of the present invention is to provide parmaceutical compositions comprising the novel benzimidazole compounds being useful for above purposes.

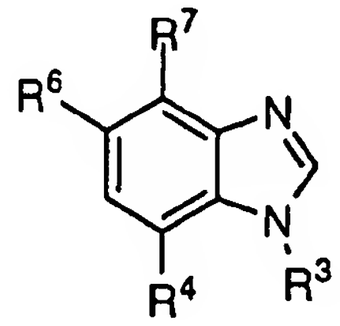
Still another object of the present invention is to provide a novel method of treating with the novel benzimidazole compounds.

Additional objects will be obvious from the following description, and others will be obvious to one skilled in the art.

Summary of the Invention

The invention then, inter alia, comprises the following, alone or in combination:

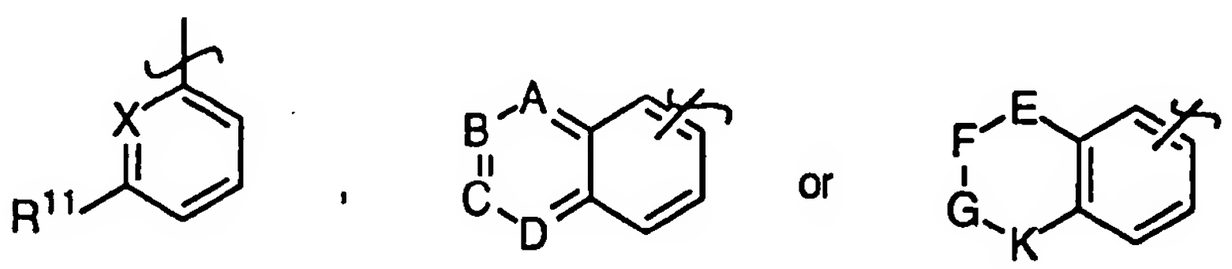
A compound having the formula:



or a pharmaceutically acceptable salt thereof

wherein

R^3 is



wherein

X is N; or C-R' wherein R' is hydrogen or together with R^4 forms a $-(NR^{111})_m-C(=O)-$, $-(NR^{111})_m-CHOH-$, or a -N=C- bridge wherein R^{111} is hydrogen or alkyl and m is 0 or 1;

one of A, B, C, and D is N and the others are CH;

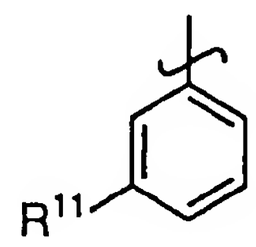
one of E, F, G, and K is N-R" wherein R" is hydrogen or alkyl and the others of E, F, G, and K are CH_2;

R^6 and R^7 are independently hydrogen; halogen; amino; nitro; cyano; acylamino; trifluoromethyl; alkyl; alkoxy; COO-alkyl; acyl; CH=NOH, CH=NO-alkyl; $CH=N-NH-(C=O)-NH_2$; phenyl which may be substituted one or more times with alkyl, nitro, halogen, or CF_3; or aryl which may be substituted one or more times with alkyl, phenyl, halogen, or CF_3; or R^6 and R^7 together forms a $(CH_2)_a-(Z)_b-(C=Y)_c-(Z')_d-(CH_2)_e$ bridge wherein each of Z and Z' independently are O, S, or NR"' wherein R"' is hydrogen or alkyl, Y is O or H_2, a and e are each independently 0, 1, 2, or 3 and b, c, and d are each independently 0 or 1 provided that the sum of a, b, c, d, and e is not larger than 6; or R^6 and R^7 together forms a -CH=CH-CH=N-, -CH=CH-N=CH-, -CH=N-CH=CH-, -N=CH-CH=CH-, or =N-S-N= bridge;

R^4 is hydrogen; amino; nitro; cyano; halogen; acylamino; phenyl which may be substituted one or more times with alkyl, amino, halogen, or CF_3; aryl which may be substituted one or more times with alkyl, phenyl, halogen, or CF_3; or R^4 together with R' forms a $-(NR^{111})_m-C(=O)-$, $-(NR^{111})_m-CHOH-$, or a -N=C- bridge wherein R^{111} is hydrogen or alkyl, and m is 1;

R^{11} is phenyl which may be substituted one or more times with alkyl, halogen, or CF_3; benzimidazolyl which may be substituted one or more times with alkyl, halogen, or CF_3; or aryl which may be substituted one or more times with alkyl, phenyl, halogen, or CF_3, amino, nitro, cyano, acylamino, trifluoromethyl; alkoxy; or acyl; provided that at least one of R^6 and R^7 is other than hydrogen, and

a compound as above wherein R^4 is hydrogen and R^3 is



wherein R^{11} is pyridyl, and

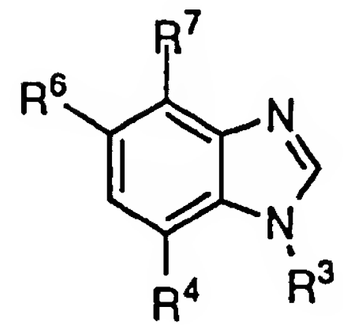
a compound as above, which is

1-[3-(3-pyridyl)-phenyl]-5-methylaldoximo-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-*i*-propyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-(2-furanyl)-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-6-iodo-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-methyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-t-butyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-phenyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-*i*-propyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-iodo-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-*t*-butyl-benzimidazole,
1-[3-(1-benzimidazolyl)-phenyl]-5-i-propyl-benzimidazole,
1-[3-(1-(2-methylimidazolyl))-phenyl]-5-phenyl-benzimidazole,
1-[3-(1-benzimidazolyl)-phenyl]-5-trifluoromethyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-(3-furanyl)-benzimidazole, or
4-trifluoromethyl-6,7-dihydro-6-methyl-7-oxo-benzimidazo-[3,4-ab][1,4]benzodiazepine,

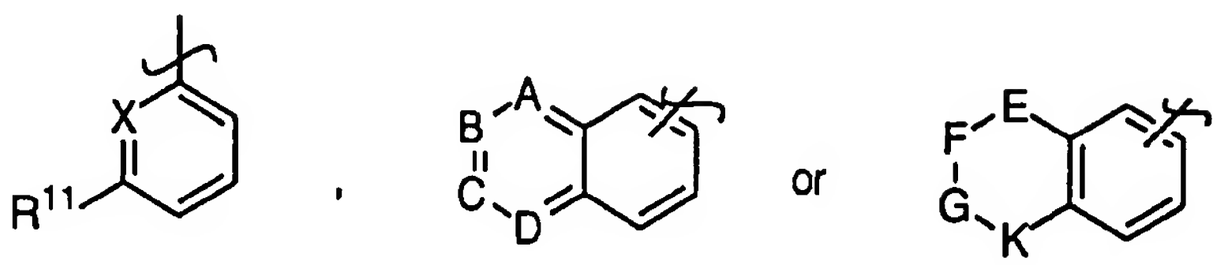
or a pharmaceutically acceptable salt thereof, and

a pharmaceutical composition comprising an effective amount of a compound as any above, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent., and

the use of a compound having the formula:

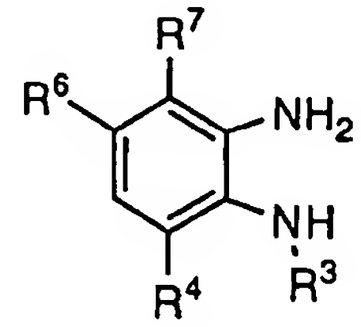


or a pharmaceutically acceptable salt thereof
wherein
R^3 is



wherein
X is N; or C-R' wherein R' is hydrogen or together with R^4 forms a $-(NR^{111})_m-C(=O)-$, $-(NR^{111})_m-CHOH-$, or a -N=C- bridge wherein R^{111} is hydrogen or alkyl and m is 0 or 1;
one of A, B, C, and D is N and the others are CH;
one of E, F, G, and K is N-R" wherein R" is hydrogen or alkyl and the others of E, F, G, and K are CH_2;
R^6 and R^7 are independently hydrogen; halogen; amino; nitro; cyano; acylamino; trifluoromethyl; alkyl; alkoxy; COO-alkyl; acyl; CH=NOH, CH=NO-alkyl; $CH=N-NH-(C=O)-NH_2$; phenyl which may be substituted one or more times with alkyl, nitro, halogen, or CF_3; or aryl which may be substituted one or more times with alkyl, phenyl, halogen, or CF_3; or R^6 and R^7 together forms a $(CH_2)_a-(Z)_b-(C=Y)_c-(Z')_d-(CH_2)_e$ bridge wherein each of Z and Z' independently are O, S, or NR"' wherein R"' is hydrogen or alkyl, Y is O or H_2, a and e are each independently 0, 1, 2, or 3 and b, c, and d are each independently 0 or 1 provided that the sum of a, b, c, d, and e is not larger than 6; or R^6 and R^7 together forms a -CH=CH-CH=N-, -CH=CH-N=CH-, -CH=N-CH=CH-, -N=CH-CH=CH-, or =N-S-N= bridge;
R^4 is hydrogen; amino; nitro; cyano; halogen; acylamino; phenyl which may be substituted one or more times with alkyl, amino, halogen, or CF_3; aryl which may be substituted one or more times with alkyl, phenyl, halogen, or CF_3; or R^4 together with R' forms a $-(NR^{111})_m-C(=O)-$, $-(NR^{111})_m-CHOH-$, or a -N=C- bridge wherein R^{111} is hydrogen or alkyl, and m is 1;
R^{11} is halogen; amino; nitro; cyano; COO-alkyl; acylamino; CF_3; alkyl; alkoxy; morpholinyl; phenyl which may be substituted one or more times with alkyl, halogen, or CF_3; benzimidazolyl which may be substituted one or more times with alkyl, halogen, or CF_3; or aryl which may be substituted one or more times with alkyl, phenyl, halogen, or CF_3, amino, nitro, cyano, acylamino, trifluoromethyl; alkoxy; or acyl, for the manufacture of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which is responsive to modulation of the benzodiazepine receptor of the central nervous system of such a living animal body, including a human, and
the use of a compound as second above for the manufacture of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which is responsive to modulation of the benzodiazepine receptor of the central nervous system of such a living animal body, including a human, and
the use of a compound as any above for the manufacture of a medicament for the treatment of anxiety, sleep disorders, memory disorders, epilepsy or any other convulsive disorder of a living animal body, including a human, and
the use as any above, wherein the compound employed is
1-[3-(3-pyridyl)-phenyl]-5-methylaldoximo-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-*i*-propyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-(2-furanyl)-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-6-iodo-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-methyl-benzimidazole,
1-[3-(1-Imidazolyl)-phenyl]-5-t-butyl-benzimidazole,
1-[3-(1-Imidazolyl)-phenyl]-5-phenyl-benzimidazole,

1-[3-(1-imidazolyl)-phenyl]-5-*i*-propyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-iodo-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-*t*-butyl-benzimidazole,
1-[3-(1-benzimidazolyl)-phenyl]-5-i-propyl-benzimidazole,
1-[3-(1-(2-methylimidazolyl))-phenyl]-5-phenyl-benzimidazole,
1-[3-(1-benzimidazolyl)-phenyl]-5-trifluoromethyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-(3-furanyl)-benzimidazole, or
4-trifluoromethyl-6,7-dihydro-6-methyl-7-oxo-benzimidazo-[3,4-ab][1,4]benzodiazepine,
or a pharmaceutically-acceptable addition salt thereof, and
a method of preparing a compound as any above, comprising the step of reacting a compound having the formula



wherein R^3, R^4, R^6 and R^7 have the meanings set forth in claim 1, with formic acid or a reactive derivative thereof, and
a method as above wherein
1-[3-(3-pyridyl)-phenyl]-5-methylaldoximo-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-*i*-propyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5(2-furanyl)-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-6-iodo-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-methyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-t-butyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-phenyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-*i*-propyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-iodo-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-*t*-butyl-benzimidazole,
1-[3-(1-benzimidazolyl)-phenyl]-5-i-propyl-benzimidazole,
1-[3-(1-(2-methylimidazolyl))-phenyl]-5-phenyl-benzimidazole,
1-[3-(1-benzimidazolyl)-phenyl]-5-trifluoromethyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-(3-furanyl)-benzimidazole, or
4-trifluoromethyl-6,7-dihydro-6-methyl-7-oxo-benzimidazo-[3,4-ab][1,4]benzodiazepine,
or a pharmaceutically-acceptable addition salt thereof, is prepared.

Halogen is fluorine, chlorine, bromine, or iodine.

Alkyl means a straight chain or branched chain of from one to eight carbon atoms or cyclic alkyl of from three to seven carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl; methyl, ethyl, propyl, isopropyl and t-butyl are preferred groups.

Alkoxy means O-alkyl, wherein alkyl is as defined above.

Acyl means (C=O)-H or (C=O)-alkyl, wherein alkyl is as defined above.

Alkylene is an alkylene group of from one to eight carbon atoms which may be straight or branched.

Acylamino is acyl-NH wherein acyl is as defined above.

Amino is NH_2 or NH-alkyl or N-$(alkyl)_2$, wherein alkyl is as defined above.

Aryl is a 5- or 6-membered heterocyclic monocyclic group. Such an aryl group includes, for example, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-oxadiazol-3-yl, 1,2,5-oxadiazol-4-yl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-4-yl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl.

Examples of pharmaceutically-acceptable addition salts include inorganic and organic acid addition salts such as the hydrochloride, hydrobromide, phosphate, nitrate, perchlorate, sulphate, citrate, lactate, tartrate,

maleate, fumarate, mandelate, benzoate, ascorbate, cinnamate, benzenesulfonate, methanesulfonate, stearate, succinate, glutamate, glycollate, toluene-p-sulphonate, formate, malonate, naphthalene-2-sulphonate, salicylate and the acetate for example.

Other acids such as oxalic acid, while not in themselves pharmaceutically acceptable may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts. Such salts are formed by procedures well known in the art.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Some of the compounds of the present invention exist in (+) and (-) forms as well as in racemic forms. Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof, with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallization of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example. The compounds of the instant invention may also be resolved by the formation of diastereomeric amides by reaction of the compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the compounds of the present invention with an optically active chloroformate or the like.

Additional methods for the resolvation of optical isomers, known to those skilled in the art may be used, and will be apparent to the average skilled in the art. Such methods include those discussed by J. Jaques, A. Collet, and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Starting materials for the processes described in the present application are known or can be prepared by known processes from commercially available chemicals.

The products of the reactions described herein are isolated by conventional means such as extraction, crystallization, distillation, chromatography, and the like.

Biology

4-aminobytyric acid (GABA) is the major inhibitory neurotransmitter and has been shown to act throughout both the central and peripheral nervous system. At present two types of GABA receptors are known, the $GABA_A$ and the $GABA_B$ receptors. Recent molecular biology has demonstrated that the $GABA_A$ receptors can be subdivided into numerous subreceptors consistant with the selective and or partial pharmacological effects observed with certain benzodiazepine receptor ligands as opposed to the unselective effects observed for the classical benzodiazepine receptor ligands such as for example diazepam. Activation of GABA receptors leads to alternations in membrane potential (hyperpolarization). The $GABA_A$ receptors are associated with chloride influx through its associated and integrated chloride channel, whereas $GABA_B$ receptor activation indirectly alters potassium and calcium channels as well as modifies second messenger production. The $GABA_A$ recognition sites can be activated by GABA, muscimol; and isoguvacine for example, but not by $GABA_B$ agonists such as for example baclofen. The modulatory $GABA_A$ recognition site at the benzodiazepine receptor sites can be selectively radiolabelled with ^3H-flunitrazepam. The affinity of various potential ligands for the benzodiazepine receptor sites can thus be evaluated by estimating the ability of test compounds to displace ^3H-flunitrazepam.

Method

Tissue preparations are performed at zero to four degrees celcius. Cerebral cortex from male Wistar rats (150-200g) is homogenized in 2 times 10 ml Tris-HCl, 30mM at pH 7.4 The resulting suspension is centrifuged at 40,000 g for 15 minutes. The pellet is washed three times with buffer, centrifuged at two degrees celcius at 40,000 g for ten minutes. The washed pellet is homogenized in 2 times 10 ml of buffer and is thereafter incubated on a water bath at 37°C for 30 minutes and is thereafter centrifuged at 40,000 g for 10 minutes. The pellet is then homogenized with buffer and is centrifuged at 0°C for 10 minutes at 40,000 g. The final pellet is resuspended in 30 ml buffer and the preparation may thereafter be stored at -20°C. In the test situation the membrane preparation is thawed and centrifuged at 2°C for ten minutes at 48,000 g. The pellet is then washed two times with 2 times 10 ml 50 mM Tris-citrate at pH 7.1 using an Ultra-Turrax homogenizer and centrifuged at 48,000 g for 10 minutes. The hereby obtained pellet is resuspended in 50 mM Tris-citrate at pH 7.1, 500 ml buffer per gram og original tissue, and is then used for binding assays. Aliquots of 0.5 ml tissue is added to

0.025 ml of ^{3}H-flunitrazepam, final concentration of 1nM, and is mixed and incubated for 40 minutes at 2°C. Non-specific binding is determined using clonazepam, at 100ng/ml final concentration. After incubation 5 ml of icecold buffer is added to the samples and these are poured directly onto Whatman GF/C glass fibre filters under suction and is immediately washed with 5 ml Icecold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non specific binding. Test value is calculated as the IC_{50} which is equivalent to the concentration which inhibits the specific binding by 50 percent.

Test results obtained by testing selected compounds of the present invention appear from the following table:

Table

Test compound:	IC_{50} (nM)
1-[3-(1-imidazolyl)-phenyl]-5-methyl-benzimidazole	1.2
1-[3-(1-imidazolyl)-phenyl]-5-t-butyl-benzimidazole	2.4
1-[3-(1-imidazolyl)-phenyl]-5-phenyl-benzimidazole	7.4
1-[3-(1-imidazolyl)-phenyl]-5-i-propyl-benzimidazole	0.6
1-[3-(3-pyridyl)-phenyl]-5-iodo-benzimidazole	1.7
1-[3-(3-pyridyl)-phenyl]-5-t-butyl-benzimidazole	10
1-[3-(1-benzimidazolyl)-phenyl]-5-i-propyl-benzimidazole	4.3
1-[3-(1-(2-methylimidazolyl)-phenyl]-5-phenyl-benzimidazole	9
1-[3-(1-benzimidazolyl)-phenyl]-5-trifluoromethyl-benzimidazole	9.2
1-[3-(3-pyridyl)-phenyl]-5-(3-furanyl)-benzimidazole	1.2
4-trifluoromethyl-6,7-dihydro-6-methyl-7-oxo-benzimidazo-[3,4-ab][1,4]benzodiazepine	5.4

Pharmaceutical Compositions

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, then it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Formulations containing one (1) milligram of active Ingredient or, more broadly, 0.01 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled In the art that the following dosage forms may comprise as the

active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from one to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting vax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting vax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated in solutions in aqueous polyethylene glycol solution.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasel cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon

(CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g. gelatin or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

Method of Treating

The compounds of this invention are extremely useful in the treatment of disorders or diseases of a living animal body due to their potent benzodiazepine receptor affinity. These properties make the compounds of this invention extremely useful in the treatment of convulsions, anxiety, sleep disorders, memory disorders as well as other disorders sensitive to benzodiazepine receptor binding activity. The compounds of this invention may accordingly be administered to a subject, including a human, in need of treatment, alleviation, or elimination of a disorder or disease associated with the benzodiazepine receptors. This includes especially convulsions, anxiety, sleep disorders and memory disorders.

Suitable dosage range are 0.01-100 milligrams daily, 0.1-50 milligrams daily, and especially 0.1-30 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

The following examples in the form of examples, methods and in the form of tables according to which compounds of the invention have been prepared will illustrate the invention further; however they are not to be construed as limiting.

EXAMPLE 1

1-(3-Iodophenyl)-5-trifluoromethylbenzimidazole (**1a**). A mixture of 2-amino-3'-iodo-4-trifluoromethyldiphenylamine (**1b**) (6.00 g, 14.4 mmol) and formic acid (60 ml) was refluxed for 16 h. After evaporation to dryness, the remanence was dissolved in ethyl acetate (100 ml) and washed with water (100 ml). The organic phase was dried and evaporated. The crude product was purified by column chromatography with methylene chloride as the eluent. Yield 4.2 g, mp 86-87°C.

EXAMPLE 2

1-(3-(1-Imidazolyl)-phenyl)-5 trifluoromethylbenzimidazole (**3a**). A mixture of **1a** (1.0 g, 2.58 mmol), imidazole (0.19 g, 2.73 mmol), potassium carbonate (0.38 g, 2.78 mmol), CuBr (20 mg, 0.15 mmol), and 1-methyl-2-pyrrolidone (5ml) was heated to 200°C for 18 hours. Dilution with water and extractive workup with ethyl acetate was followed by chromatography on silica gel. Yield: 0.43 g, mp. 177-180°C.

EXAMPLE 3

2-Amino-3'-iodo-4-trifluoromethyldiphenylamine hydrochloride (**1b**). A mixture of **1c** (6.0 g, 14.7 mmol), sodium sulfide nonahydrate (9.8 g, 44 mmol), ammonium chloride (2.35 g, 44 mmol), and 99% ethanol (100 ml) was refluxed under nitrogen for 3 hours. After cooling to room temperature the reaction mixture was poured into water (400ml) and extracted with ethyl acetate. The organic phase was washed with water, dried and con-

centrated. The remanence was purified by column chromatography. The product was converted to the hydrochloride by addition of methanolic hydrogen chloride to the eluate followed by evaporation of the solvent. Yield 6.0 g, mp. 182-185°C.

EXAMPLE 3a

Identical to Example 3 except for the products being isolated as the free bases.

EXAMPLE 4

2-amino-3'-(1-imidazolyl)-4-*i*-propyldiphenylamine hydrochloride (**14b**). A mixture of **14c** (1g, 3.11mmol) and palladium on activated carbon (5%, 0.1g) in MeOH (25ml) was hydrogenated at ambient pressure until the hydrogen uptake had ceased. The reaction mixture was filtered through celite into a few milliliters of etheral hydrogen chloride. Evaporation of solvent left **14b** (0.95g, 2.89mmol). Mp. 185-190°C.

EXAMPLE 4a

Identical to Example 4 except for the products being isolated as the free bases.

EXAMPLE 5

3-Iodo-2-nitro-4-trifluoromethyldiphenylamine (**1c**). To a mixture of 3-iodoaniline (11.0g, 50mmol) and 4-chloro-3-nitrobenzotrifluoride (11.3g, 50mmol) in dry DMF (50ml) under nitrogen, was added sodium hydride (2.55g, 85mmol) in small portions over 0.5 hours. The reaction mixture was stirred at room temperature for 12 hours. The mixture was poured into water (200ml). Diethyl ether (300ml) was added and the phases were separated. The etheral phase was washed with water (3x200ml), dried and evaporated. The crude product was purified by column chromatography using petroleum ether/methylenechloride (4:1) as the eluent. The crystalline product was triturated with petroleum ether and filtered. Yield 12.6g, mp. 98-101°C.

EXAMPLE 5a

As Example 5 but with dry potassium carbonate as the base and a reaction temperature of 120°C.

EXAMPLE 6

3'-Bromo-4-*t*-butyl-2-nitrodiphenylamine (**6d**). 4-*t*-Butyl-2-nitroaniline (see Example 7) (2g, 10.31mmol), 3-bromo-1-iodobenzene (5.84g, 20.62mmol), potassium carbonate (1.52g, 11mmol) and Cu-bronze (20mg) were thoroughly mixed and heated to 160°C overnight. After cooling the reaction mixture was partitioned between water and toluene. The organic phase was dried with $MgSO_4$ and evaporated. The remanence was passed through a silica gel column with ethyl acetate/petroleum ether (1:9) as the eluent to yield **6d** (2.27g, 61%). Mp 86-87°C.

EXAMPLE 7

4-*t*-Butyl-2-nitroaniline. 4-*t*-Butylaniline (5g, 33.58mmol) in acetic anhydride (25ml) was stirred at ambient temperature for 0.5h. The mixture was cooled in an ice-bath and nitric acid (6ml, 65%) was added at such a rate that the temperature did not exceed 18°C. Following the addition the mixture was poured on ice (200g). The precipitate was filtered off, washed thoroughly with water and dried to yield N-acetyl-4-*t*-butyl-2-nitroaniline (7.15g, 90%). Mp. 109-110°C.

This product (7g, 29.66mmol) was heated to reflux in sulfuric acid (30ml, 70%) for 0.5h. After cooling water (100ml) was added. The product was filtered off, washed with water and air-dried to yield 4-*t*-butyl-2-nitroaniline (5.4g, 94%). Mp. 107-108°C.

EXAMPLE 8

4-Acetaminobiphenyl. 4-Aminobiphenyl (15g, 88.76mmol) in toluene (250ml) was added acetic anhydride (8.5ml, 90mmol). The mixture was stirred at ambient temperature for 1 hour. Following the reaction the mixture was poured into petroleum ether (500ml), the product was filtered off, washed with petroleum ether and dried

to yield 4- acetaminobiphenyl (18.7g).

4-Acetamino-3-nitrobiphenyl. 4-Acetaminobiphenyl (17g, 80.57mmol) in glacial acetic acid (600ml) was added a solution of potassium nitrate (18g, 178mmol) in conc. sulphuric acid (75ml) at such a rate that the temperature was kept below 30°C. Following the addition the mixture was stirred at ambient temperature for 72 hours. The reaction mixture was poured into ice-water (1200ml). The product was filtered off, washed thoroughly with water and dried. Recrystallization from EtOH (99%, 150ml) afforded 4-acetamino-3-nitrobiphenyl (8.7g).

4-Amino-3-nitrobiphenyl. A mixture of N-acetyl-4-amino-3-nitrobiphenyl (8.5g, 33.2mmol), aqueous sodium hydroxide (100ml, 1M) and dimethoxyethane (75ml) was stirred at ambient temperature overnight. The mixture was poured into water (300ml). The product was filtered off, washed with water and dried to yield 4-amino-3-nitrobiphenyl (7g, 32.7mmol). Mp. 157-159°C.

EXAMPLE 9

2,6-Dinitro-4-trifluoromethyldiphenylamine (**4k**). 4-Chloro-3,5-dinitrobenzoetrifluoride (5g, 18.5mmol) in DMF (25ml) was added aniline (3.7ml, 40mmol) at 5°C. The mixture was allowed to warm to room temperature. After complete reaction the mixture was poured into water (100ml). The product was filtered off, washed with water and dried to yield the orange crystalline product. Yield 6.9g. Mp 118-120°C.

2-Amino-6-nitro-4-trifluoromethyldiphenylamine (**4j**). From **4k** as described in Example 3. Mp 140-143°C.

7-Nitro-1-phenyl-5-trifluoromethylbenzimidazole (**4i**). From **4j** as described in Example 1. Mp 95-98°C

7-Amino-1-phenyl-5-trifluoromethylbenzimidazole hydrochloride(**4h**). From **4i** as described in Example 4.

7-Iodo-1-phenyl-5-trifluoromethylbenzimidazole (**4g**). To a cooled suspension of **4h** (4.8g, 15mmol) in a mixture of water (12ml) and conc. hydrochloric acid (20ml) was added a solution of sodium nitrite (1.2g, 17mmol in 5ml water) at such a rate that the temperature was kept below 5°C. Following the addition the mixture was stirred for 10min. and a solution of potassium iodide (4g, 24mmol in 10ml water) was added carefully. The mixture was left at ambient temperature until the evolution of nitrogen had ceased (approx. 2h). Aqueous sodium sulphite was added and the product was filtered off. Purification was achieved by column chromatography on silica gel using a mixture of ethyl acetate and petroleum ether (1:9) as the eluent. Yield 1.3g. Mp 118-120°C.

EXAMPLE 10

5-Amino-1-(3-(3-pyridyl)phenyl)benzimidazole (**19a**). **24a** (1g, 3.16mmol) in conc. hydrochloric acid (10ml) was added tin(II)chloride (1.98g, 10.43mmol) and was refluxed overnight. After cooling the mixture was poured into water (50ml). Following filtration the filtrate was cooled in an ice-bath and rendered alkaline by addition of 12M sodium hydroxyde. A small volume of ethanol was added and the mixture was stirred at 0°C until a homogeneous suspension was obtained. The product was filtered off, washed with water and air-dried. Yield 0.9g. Mp 172-175°C.

EXAMPLE 11

1-(3-(3'-Amino)biphenylyl)-5-*t*-butylbenzimidazole (**20a**). **43a** (1g, 3.04mmol), sodium bicarbonate (1.28g, 15.2mmol), 3-aminophenylboronic acid and tetrakis(triphenylphosphine)palladium (30mg) was added to a mixture of water (10ml) and dimethoxyethane (20ml) under a stream of nitrogen. The reaction mixture was heated to 80°C overnight, cooled to room temperature and poured into water (100ml). A small volume of ethyl acetate was added and the mixture was stirred until the product had precipitated. Filtration and column chromatography on silica gel using ethyl acetate/petroleum ether (1:9) as the eluent yielded **20a** (0.52g. Mp 162-164°C).

EXAMPLE 12

1-(3-Bromophenyl)-5-dimethylaminobenzimidazole hydrochloride (**23a**). **25a** (0.8g, 2.78mmol) in DMF (10ml) was added potassium carbonate (0.83g, 6mmol) and iodomethane (0.36ml, 5.83mmol) and was stirred at ambient temperature for 4 hours. The mixture was poured into water (80ml) and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, concentrated to a small volume and eluted through silica gel with ethyl acetate/petroleum ether (1:9). The solvent was evaporated and the oily product was dissolved in dry diethyl ether and precipitated as the hydrochloride on addition of etheral hydrochloric acid (2M). The product was filtered off and dried under nitrogen. Yield 0.21g. Mp 146-150°C.

EXAMPLE 13

5-*t*-Butyl-1-(5-(3-(2-pyridyl)oxadiazolyl))benzimidazole (**26a**). **44a** (0.75g, 2.55mmol) in THF (30ml) was heated to reflux. Carbonyldiimidazole (0.75g, 4.5mmol) was added and reflux was maintained for 1 hour. To 10ml of this solution pyridin-2-carbamidoxime (0.28, 2mmol) was added and the mixture was heated to reflux for 2 hours. After evaporation of the solvent, toluene (5ml) was added and the mixture was refluxed overnight. Removal of solvent left a crude product which precipitated upon trituration with water. The product was filtered off, dried and washed with petroleum ether. Yield 0.29g. Mp 139-141°C.

Compounds **27a-30a** and **33a** were prepared analogueously from the appropiate carbamidoximes.

EXAMPLE 14

3-(4-Morpholinyl)nitrobenzene. 3-Nitroaniline (10g, 72mmol) in DMF (100ml) was added bis(2-chloroethyl) ether (11.7ml, 100mmol) and potassium carbonate (27.6g, 200mmol). The mixture was heated to reflux for 10 hours. Additional bis(2-chloroethyl) ether (3ml) was added and reflux was maintained for 18 hours. Addition of bis(2-chloroethyl) ether was repeated and reflux was continued for 4 hours. The solvent was evaporated and the residue partitioned between water and ethyl acetate. The organic phase was dried and evaporated. The residue was extracted with diethyl ether. The extract was concentrated and purified by column chromatography on silica gel with ethyl acetate/petroleum ether (3:7) as the eluent. Yield 3.4g. Mp 87-90°C.

3-(4-Morpholinyl)aniline. 3-(4-Morpholinyl)nitrobenzene (1.9g, 9.1mmol) was hydrogenated as described in Example 4. Yield 1.27g. Mp 115°C.

4-*t*-Butyl-3'-(4-morpholinyl)-2-nitrodiphenylamine (**32c**). 4-*t*-Butyl-1-iodo-2-nitrobenzene* (3g, 10mmol), 3-(4-morpholinyl)aniline (1.2g, 6.7mmol), potassium carbonate (1.38g, 10mmol) and Cu-bronze (30mg) was thoroughly mixed and heated to 170°C for 5 hours. The product was isolated and purified as described in Example 6. Yield 0.2g oily product.

* 4-*t*-Butyl-1-iodo-2-nitrobenzene was prepared from 4-*t*-butyl-2-nitroaniline (Example 7) in analogy with **4g** (Example 9).

EXAMPLE 15

N,*N*'-Bis(2-nitro-4-trifluoromethyl)-1,3-phenylenediamine (**42c**) and *N*-(2-nitro-4-trifluoromethyl)-1,3-phenylenediamine (**45c**). 4-Chloro-2-nitrobenzoetrifluoride (7.6ml, 50mmol) in dry DMF was added triethyl amine (7ml, 50mmol) and 1,3-phenylenediamine (3.24g, 30mmol). The mixture was heated to 80°C overnight and then to 120°C for 6 hours. The solvent was evaporated and the residue was partitioned between water and diethyl ether. The organic phase was dried and concentrated and the product mixture was separated by column chromatography on silica gel using diethyl ether/petroleum ether (1:1) as the eluent. Yield of **42c**: 3.7g, mp 133-135°C. Yield of **45c**: 3.7g, mp 110-112°C.

N-(2-Nitrophenyl)-*N*'-(2-nitro-4-trifluoromethylphenyl)-1,3-phenylenediamine (**39c**). **45c** (2g, 6.7mmol), 1-fluoro-2-nitrobenzene and potassium carbonate (1g, 7mmol) were thoroughly mixed and heated to 180°C for 3 days. After cooling the reaction mixture was partitioned between water and ethyl acetate. The organic phase was dried, concentrated and extracted with diethyl ether. The etheral extract was passed through a short silica gel column to yield **39c**, 0.8g. Mp 95-98°C.

EXAMPLE 16

N-(Acetyl)-*N*'-(2-nitro-4-trifluoromethyl)-1,3-phenylenediamine (**40c**). **45c** (1.7g, 5.7mmol) and triethyl amine (0.84ml, 6mmol) in THF (20ml) was added acetylchloride (0.4ml, 6mmol). Following the addition water was added and the mixture was allowed to stir for 15min. The product was filtered off and air-dried. Mp 188-190°C.

EXAMPLE 17

4-*t*-Butyl-3'-carboxy-2-nitrodiphenylamine (**44c**). 4-*t*-Butyl-2-nitroaniline (see Example 7), 3-iodobenzoic acid (10g, 40mmol), potassium carbonate (5.5g, 40mmol) and a catalytic amount of CuI were thoroughly mixed and heated to 230°C for 4 hours. The reaction mixture was allowed to cool to 100°C and water was added. After cooling to room temperature the solution was rendered acidic by careful addition of glacial acetic acid. The precipitate was filtered off and washed with dichloromethane. Recrystallization from 2-propanol afforded **44c**. Yield 4.3g. Mp 194-195°C.

EXAMPLE 18

3-Acetyl-1,2-phenylendiamine hydrochloride was prepared from 3-acetyl-2-nitroaniline as described in Example 4. Mp 246-250°C.

4-Acetylbenzimidazole was prepared from 3-acetyl-1,2-phenylendiamine as described in Example 1. Mp 220-223°C.

4-Acetyl-1-(3-nitrophenyl)benzimidazole (3g). 4-Acetylbenzimidazole (4.4g, 27.5mmol) was dissolved in dry DMSO (40ml) and cooled. Sodium hydride (0.91g, 80% suspension in oil) was added and the mixture was allowed to warm to room temperature. When the evolution of hydrogen had ceased 1-fluoro-3-nitrobenzene was added and the mixture was heated to 120°C overnight. After cooling the reaction mixture was poured into ice-water and the crude product was filtered off. Purification was achieved by column chromatography on silica gel with ethyl acetate/petroleum ether (1:1) as the eluent. Yield 2.09g, mp 175-177°C.

EXAMPLE 19

4-Nitrobenzimidazole was prepared from 3-nitro-1,2-phenylendiamine as described in Example 1. Mp 242-245°C.

4-Nitro-1-(3-nitrophenyl)benzimidazole was prepared analogueously to **3g** from 4-nitrobenzimidazole and 1-fluoro-3-nitrobenzene. Mp 260-262°C.

1-(3-Aminophenyl)-4-nitrobenzimidazole was prepared from 4-nitro-1-(3-nitrophenyl)benzimidazole as described in Example 3a. Mp 159-161°C.

4-Nitro-1-(3-pivaloylaminophenyl)benzimidazole (**5g**). 1-(3-Aminophenyl)-4-nitrobenzimidazole (0.15g, 0.6mmol) was suspended in THF (4ml). Triethyl amine (0.084ml, 0.6mmol) and pivaloylchloride (0.074ml, 0.6ml in 1ml THF) was added. After stirring for 3 hours at room temperature another equivalent of pivaloylchloride was added and the temperature was raised to 70°C for 0.5 hours. After evaporation of solvent the residue was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent was removed by evaporation. Trituration with petroleum ether containing a few percent dichloromethane afforded **5g**. Yield 0.12g, mp 105-110°C.

EXAMPLE 20

4-*t*-Butyl-1-fluorobenzene. 4-*t*-Butylaniline (14.9g, 100mmol) was suspended in aqueous hydrochloric acid (50ml, 6M) at 5°C. Sodium nitrite (7.6g, 110mmol in 10ml water) was added at such a rate that the temperature was kept between 5-7°C. Following the addition the resulting solution was stirred for 15 min. and sodium tetrafluoroborate (15.4g, 140mmol in 30ml water) was added at 5-8°C. The mixture was stirred for 15 min. 4-*t*-Butylbenzenediazonium tetrafluoroborate was filtered off, dried with suction and washed with diethyl ether to yield 20.96g. This diazonium salt was decomposed by heating to 140°C on an oil-bath. The product was distilled off at reduced pressure. Yield 11.15g colorless oil.

4-*t*-Butyl-1-fluoro-2-nitrobenzene. 1-Fluoro-4-*t*-butylbenzene (10g, 65.79mmol) was dissolved in concentrated sulfuric acid (40ml) at 0°C. Solid potassium nitrate (6.64g, 65.79mmol) was added in small portions during 1 hour. The temperature was kept below 5°C. Following the addition stirring was continued for 2 hours. The reaction mixture was poured into ice-water (400ml) and extracted with dichloromethane (3x50ml). The organic phase was washed with water, aqueous sodium bicarbonate (1M) and water successively, dried over $MgSO_4$ and filtered through silica gel (5g). Evaporation of solvent left the crude product (10.32g). Column chromatography on silica gel using petroleum ether containing 1% dichloromethane as the eluent afforded the pure product (7.6g colorless oil).

N-(2-Bromo-6-pyridyl)-4-*t*-butyl-2-nitroaniline. 4-*t*-Butyl-1-fluoro-2-nitrobenzene (1.97g, 10mmol), 2-amino-6-bromopyridine (1.73g, 10mmol) and potassium carbonate (1.38g, 10mmol) were thoroughly mixed and heated to 150°C overnight. The temperature was raised to 180°C for 30 hours. After cooling water and a small amount of ethyl acetate was added and the mixture was stirred for 1 hour. The organic phase was dried and concentrated and eluted through silica gel with petroleum ether/diethyl ether (9:1). Yield: 1.25g, mp 78-81°C.

2-Amino-*N*-(2-bromo-6-pyridyl)-4-*t*-butylaniline was prepared from *N*-(2-bromo-6-pyridyl)-4-*t*-butyl-2-nitroaniline (1.25g, 3.57mmol) as described in Example 3. Yield: 0.85g, mp 125-128°C.

1-(2-Bromo-6-pyridyl)-5-*t*-butylbenzimidazole (**6g**) was prepared from 2-Amino-*N*-(2-bromo-5-pyridyl)-4-

t-butylaniline (0.8g) as described in Example 1. Yield: 10mg* , mp 98-100°C.

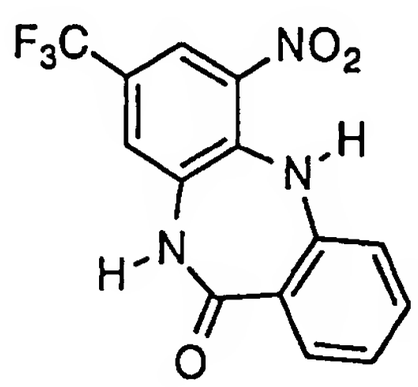
EXAMPLE 21

1-(3-Bromophenyl)-4-nitrobenzimidazole (**7g**). 4-Nitrobenzimidazole (see Example 19. 0.75g, 4.6mmol), 1,3-dibromobenzene (1.11ml, 9.2mmol), potassium carbonate (0.64g, 4.6mmol) and a catalytic amount of Cu-bronze were mixed in dry 1-methyl-2-pyrrolidone (2ml) and heated to 140°C for 3 days. One equivalent of 1,3-dibromobenzene was added and heating was continued for 24 hours. The cooled reaction mixture was extracted with ethyl acetate. The extract was dried and concentrated and eluted through silica gel with ethyl acetate/methanol (9:1) to yield **7g** (33mg, mp 180-182°C).

EXAMPLE 22

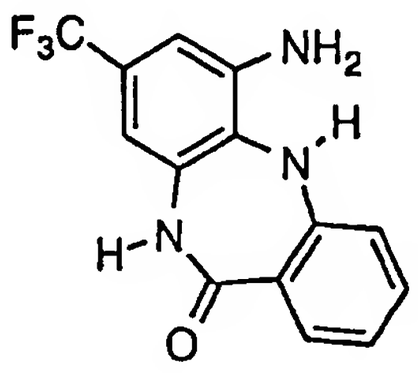
Ethyl *N*-(2,6-dinitro-4-trifluoromethylphenyl)anthranilate (**1i**). To a mixture of 4-chloro-3,5-dinitrobenzoetrifluoride (6.76g, 25mmol) and ethyl anthranilate (3.7ml, 25mmol) in dry DMF (20ml) was added sodium hydride (30mmol, 1.2g 60% suspension in oil) in small portions. The mixture was stirred at 80°C overnight, cooled and poured into ice-water (400ml). The product was filtered off, washed with water and dried. Recrystallization from ethanol (200ml) yielded **1i** (7.27g, mp 152-154°C).

1j. **1i** (3.42g, 8.56mmol) and ammonium chloride (1.37g, 25.7mmol) in ethanol (50ml) was added a solution of sodium sulfide nonahydrat (6.17g, 25.7mmol in 50ml ethanol) at 0°C. The mixture was allowed to heat to room temperature. After 1 hour the mixture was filtered and the filtrate was evaporated to dryness. Trituration of the residue with ethyl acetate/ petroleum ether (1:9) and diethyl ether successively afforded **1j**. Yield: 2.28g, mp 285-293°C.



1j

1h. **1j** (1.43g, 4.42mmol) was hydrogenated as described in Example 4. The product was isolated as the free base. Yield: 0.66g.



1h

1f (see Table 5 for structure)was prepared from **1h** (0.66g, 2.24mmol) as described in Example 1. Yield: 0.42g, mp 330-332°C.

* Most of the starting material was formylated without ring-closure.

EXAMPLE 23

2f. (see Table 5 for structure) **1f** (1g, 3.3mmol) in dry DMF (10ml) was added sodium hydride (0.1g, 3.3mmol) at 0°C. Following the addition the mixture was stirred at ambient temperature for 20min. Iodomethane (0.52g, 3.66mmol) was added and stirring was continued for 4 hours. The reaction mixture was poured into water (40ml), the product was filtered off and dried. Trituration with dry diethyl ether yielded **2f** (0.37g, mp 197-198°C).

EXAMPLE 24

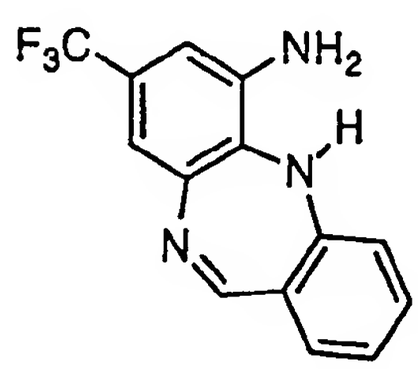
4f (see Table 5 for structure). **2f** (0.1g, 0.33mmol) in dry THF (4ml) was added $LiAlH_4$ (10mg, 0.33mmol) at 0°C. The reaction mixture was stirred for 15min. and poured into ice-water (10ml). The product was filtered off and dried to yield **4f** (0.1g, mp 169-170°C).

EXAMPLE 25

2',6'-Dinitro-2-hydroxymethyl-4'-trifluoromethyldiphenylamine (5j). A mixture of 4-chloro-3,5-dinitrobenzoetrifluoride (10g, 36.96mmol), 2-hydroxymethylaniline (5g, 40.66mmol) and potassium carbonate (5.1g, 36.96mmol) in DMF (250ml) was stirred at ambient temperature for 1.5 hours. The reaction mixture was poured into ice-water (1l) and the product was filtered off. Trituration with petroleum ether containing a small amount of dichloromethane afforded **5j** (9.73g, mp 117-120°C).

2',6'-Dinitro-2-(4-toluensulfonyloxymethyl)-4'-trifluoromethyldiphenylamine (5l). **5j** (9g, 25.19mmol) in pyridine (55ml) was added 4-toluenesulfonyl chloride in small portions at ambient temperature. Following the addition the mixture was stirred at 40°C overnight, poured into ice-water and acidified with hydrochloric acid. The product was extracted with ethyl acetate and isolated by evaporation of the solvent. Trituration with diethyl ether afforded pure **5l**. Yield 13.49g.

5h. **5l** (7g, 13.69mmol) and ammonium chloride (4.4g, 82.12mmol) in ethanol (250ml) was added sodium sulfide (19.7g, 82.12mmol) in small portions at 0°C. Following the addition the mixture was stirred at ambient temperature for 5 hours. Filtration and evaporation of solvent left a crude product, which upon extraction with diethyl ether and column chromatography on silica gel using ethyl acetate/petroleum ether (1:1) as the eluent afforded pure **5h** (1.51g, mp 135-138°C):



5h

5f (see Table 5 for structure). **5h** (1.46g, 5.23mmol) was refluxed in formic acid (50ml) for 1.5 hours. The cooled mixture was poured into water (200ml) and extracted with ethyl acetate. The extract was eluted through silica gel with ethyl acetate to yield a formylated product which upon reflux in ethanolic sodium hydroxide afforded **5f**. Yield 0.58g, mp 242-243°C.

EXAMPLE 26

N-(4-Methyl-2-nitrophenyl)anthranilic acid (6j). 2-Iodobenzoic acid (5g, 20.16mmol), 4-methyl-2-nitroaniline (6.12g, 40.32mmol), potassium carbonate (2.8g, 20.3mmol) and CuI (0.2g) were thoroughly mixed and heated to 200°C for 1 hour. After cooling the solid reaction mixture was partitioned between ethyl acetate and aqueous sodium hydroxide (1M). The product precipitated from the aqueous phase on acidification with hydrochloric acid (4M). Yield 3.69g, mp 209-213°C.

9,10-Dihydro-2-methyl-4-nitroacredin-9-one (6l). **6j** (2.56g, 9.41mmol) was heated to 100°C in conc. sulfuric acid (6ml) for 1 hour. After cooling the mixture was poured into ice-water (50ml). The product was filtered

off, washed with water and air-dried. Quantitative yield, mp 232-234°C.

9,10-Dihydro-4-amino-2-methylacredin-9-one (**6h**) was prepared from **6i** (2g, 7.87mmol) as described in Example 3. Yield 1.4g, mp 292-297°C.

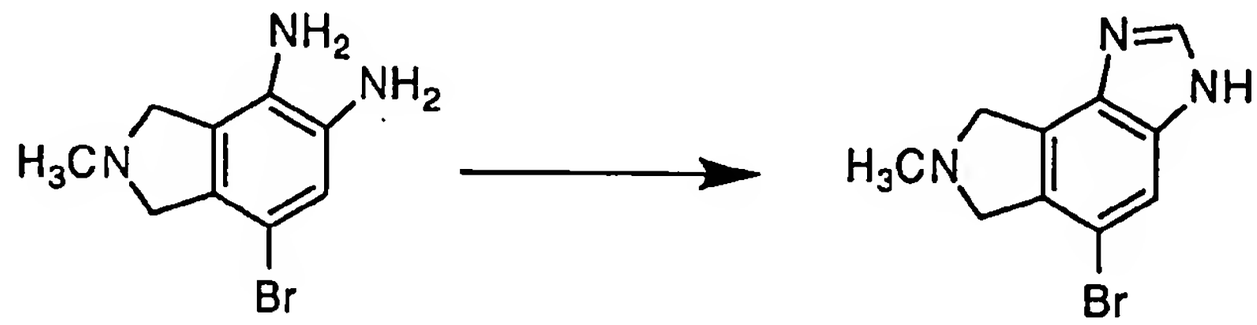
6f (see Table 5 for structure) was prepared from **6h** (1g, 4.46mmol) as described in Example 1. Yield after recrystallization from ethanol: 0.4g, mp 255-257°C.

EXAMPLE 27

Imidazolo[6,7-d]phthalide (**3h**) was prepared from 6,7-diaminophthalide (3.7g, 22.57mmol) as described in Example 1. Yield 3.8g, mp 280°C.

6-(3-nitrophenyl)imidazolo[6.7-d]phthalide (**3e**). **3h** (0.45g, 2.5mmol) in dry DMSO was added sodium hydride (0.1g 80% suspension in oil). After the evolution of nitrogen had ceased 3-fluoronitrobenzene (0.32ml, 3mmol) was added and the mixture was stirred at 120°C for 2 days. After cooling water and a few drops of glacial acetic acid was added. The product was filtered off and purified by column chromatography on silica gel using dichloromethane/aceton (9:1) as the eluent. Yield 9mg, Mp 266-268°C.

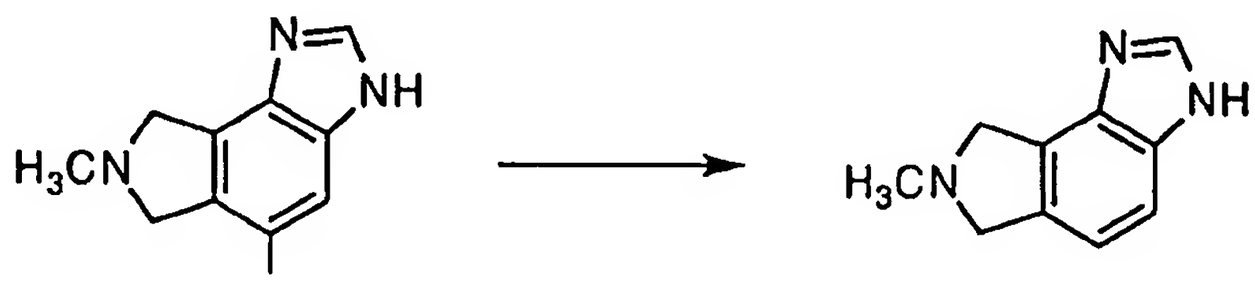
EXAMPLE 28



5-bromo-6,8-dihydro-7-methyl-2H-pyrrolo[3,4-e]benzimidazole.

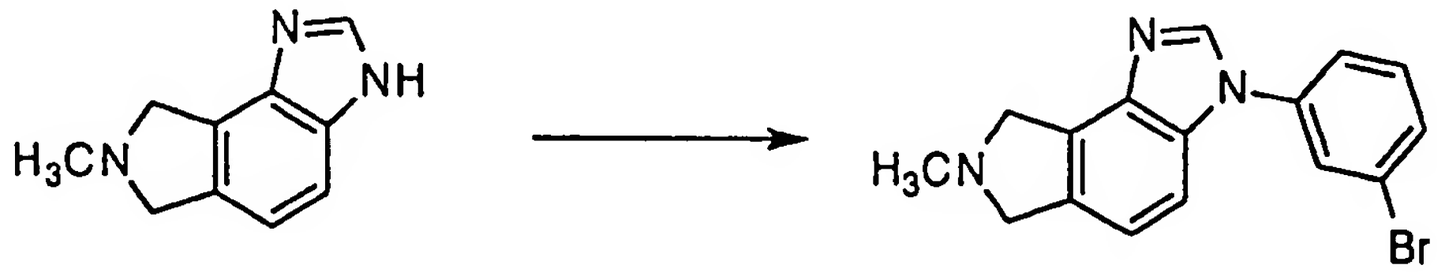
A solution of 7-bromo-2,3-dihydro-2-methyl-1H-isoindole (0.6g) in formic acid (10 ml) was refluxed for 5 hours, whereafter it was evaporated to dryness. The residue was treated with a mixture of water/EtOAc (5/5 ml). pH was adjusted to 9 with sodium carbonate, whereby the title compound precipitated as pale crystals. Mp. 225-227°C.

EXAMPLE 29



The above product was hydrogenated under standard conditions to give 2,3-dihydro-2-methyl-1H-isoindole hydrobromide with Pd/C as the catalyst. Mp. > 300°C.

EXAMPLE 30



3-(3-bromophenyl)-6,8-dihydro-7-methyl-2H-pyrrolo[3,4-e]benzimidazole.

A mixture of 6,8-dihydro-7-methyl-2H-pyrrolo[3,4-e]benzimidazole (0.25g), K_2CO_3 (0.26g), 3-bromo-1-iodobenzene (0.8g) and Copper powder (15-20mg) was heated in N-methyl-2-pyrrolidone (5ml) at 180°C for 3

hours. The mixture was then partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4 and evaporated. The oily residue was purified on SiO_2 with EtOAc as the eluent. ^{1}H-NMR (500MHz,$CDCl_3$) ppm: 2.8(s,3H), 4.2(s,2H), 4.45(s,2H), 7.2-7.7(m,6H aromatic) 8.1(s,1H imidazole).

EXAMPLE 31

3-(3-Nitrophenyl)-benzo[e]benzimidazole (**2k**). To **3k** (2.2g, 13mmol) in dry DMSO (30ml) was added sodium hydride (0.43g 80% in oil, 14.3mmol) at 0°C. When evolution of hydrogen had ceased 3-fluoronitrobenzene (1.52ml, 14.3mmol) was added and the mixture was heated to 110-120°C for 2 days. After cooling the mixture was diluted with 4 volumes of water and extracted with ethyl acetate. Drying and evaporation of solvent followed by trituration with ethanol left **2k** as yellow crystals (1.49g, 40%). Mp 136-138°C.

3-(3-Nitrophenyl)-pyrido[1,3-e]benzimidazole (**4k**) was prepared analogueously from **5k** (0.7g, 4.14mmol). Yield 0.25g (21%). Mp 219-221°C.

3-(3-nitrophenyl)-7-methyl-piperido[3,4-e]benzimidazole hydrochloride (**6k**) was prepared analogueously from **7k** (1.56g, 7mmol) using two equivalents of sodium hydride. Yield 70mg (3%). Mp 266-269°C.

EXAMPLE 32

1,2-Diaminonaphtalene hydrochloride was prepared analogueously to 2-methyl-1,2,3,4-tetrahydroisoquinoline as described in United States patent application Ser. No. 08/124,770 of September 24, 1993. Mp 223-226°C.

5,6-Diaminoquinoline hydrochloride was prepared from 5-amino-6-nitroquinoline (1g, 5.29mmol) as described in Example 4. Yield 1.0g (97%). Mp 214-220°C.

EXAMPLE 33

1-(3-(3-pyridyl)phenyl)-5-hydroxymethylbenzimidazole (**49a**). **48a** (3.5g, 9.8mmol) in dry THF (25ml) was added $LiAlH_4$ (0.36g, 4.9mmol) portionswise during 1 hour at 0°C under N_2. Following the addition the mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried with $MgSO_4$ and evaporated. The residue was eluted through silica gel with EtOH/MeOH mixture (9:1). Evaporation of solvent from the pure fractions left **49a**. Yield 1.58g (54%). Mp 183-185°C.

EXAMPLE 34

1-(3-(3-pyridyl)phenyl)-5-formylbenzimidazole (**50a**). **49a** (0.68g, 2.26mmol) in toluene (5ml) was added benzeneseleninic acid (0.64g, 3.39mmol). The mixture was heated to 70°C for 5 hours. After cooling the product was filtered off and washed with warm toluene and CH_2Cl_2 successively. Yield 0.58g (86%). Mp 200-202°C.

EXAMPLE 35

1-(3-(3-pyridyl)phenyl)-5-aldoximobenzimidazole (**52a**). **50a** (0.25g, 0.84mmol) in abs. EtOH (10ml) was added hydroxylamine hydrochloride (0.17g, 2.48mmol). The suspension was heated to 70°C for 30 min. After cooling water was added. The product was filtered off, washed with water and air-dried to yield **52a** (0.14g, 53%). Mp 228-230°C.

EXAMPLE 36

1-(3-(3-pyridyl)phenyl)-5-semicarbazonobenzimidazole (**55a**). Analogueously to **52a** with addition of one equivalent pyridine to the reaction mixture. Yield 0.18g (60%). Mp 275-278°C.

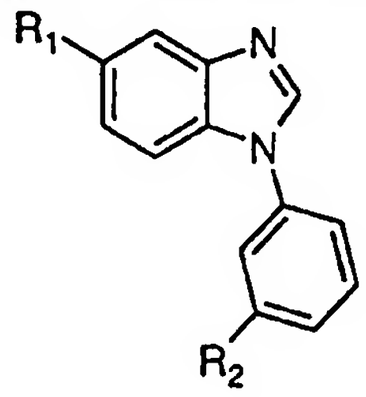
EXAMPLE 37

1-Phenyl-5-trifluoromethyl-7-benzoylaminobenzimidazole (**15g**). **14g** (0.3g, 1.08mmol) in THF (10ml) was added triethylamine (0.3ml) and benzoylchloride (0.23ml). The mixture was stirred at ambient temperature overnight. The solvent was removed *in vacuo* and the remanence was partitioned between water and ethyl acetate. The organic phase was dried and evaporated. The oily residue was dissolved in diethyl ether, and the product precipitated upon addition of petroleum ether. Yield 0.15g (36%). Mp 152-155°C.

EXAMPLE 38

1-(3-Bromophenyl)-5-methoxymethylbenzimidazole (66a). **65a** (1g, 3.3mmol) in dry DMF (10ml) was added sodium hydride (0.11g 80% in oil, 3.63mmol) at 0°C. When evolution of hydrogen had ceased iodomethane (0.23ml, 3.63mmol) was added, and the mixture was stirred at 40°C for 1 hour. Dilution with water and extractive workup with ethyl acetate followed by column chromatography on silica gel, using ethyl acetate as the eluent, afforded **66a** as a colorless oil. Yield 0.52g (59%).

Table 1. Compounds 1a-66a.



No.	R_1	R_2	Mp/°C	Starting material	Example
1a	CF_3	I	86-87	1b	1
2a	Me	CN	142-143	2b	1
3a	CF_3	1-imidazolyl	177-180	1a	2
4a	*i*-PrO_2C	1-imidazolyl	125-128	4b	1
5a	Me	1-imidazolyl	167-168	5b	1
6a*	*t*-Bu	1-imidazolyl	200-210	6b	1
7a	*t*-Bu	1-(4-phenylimidazolyl)	175-177	7b	1
8a*	*t*-Bu	1-(4-methylimidazolyl)	215-225	8b	1
9a	Ph	1-imidazolyl	163-164	9b	1
10a	n-Bu	1-imidazolyl		10b	1
11a	n-Bu	1-(4-phenylimidazolyl)		11b	1
12a	n-Bu	1-(2-methylimidazolyl)		12b	1
13a*	$(CH_2)_5CH$	1-imidazolyl	222-225	13b	1
14a*	*i*-Pr	1-imidazolyl	208-212	14b	1
15a	*i*-Pr	1-(4-phenylimidazolyl)	215-218	15b	1
16a	*i*-Pr	1-(2-methylimidazolyl)		16b	1
17a	NO_2	1-benzimidazolyl	237-240	31a	2
18a	I	3-pyridyl	200-202	19a	9
19a	NH_2	3-pyridyl	172-175	24a	10
20a	*t*-Bu	3-aminophenyl	162-164	43a	11
21a	*t*-Bu	3-furanyl	118-120	43a	11[b]
22a	*t*-Bu	3-pyridyl	137-140	43a	11[c]
23a*	NMe_2	Br	146-150	25a	12
24a	NO_2	3-pyridyl	229-230	31a	11[c]
25a	NH_2	Br	140-142	31a	10
26a	*t*-Bu	5-(3-(2-pyridyl)oxadiazolyl)	139-141	44a	13
27a	*t*-Bu	5-(3-(3-pyridyl)oxadiazolyl)	138-143	44a	13

28a	*t*-Bu	5-(3-(4-pyridyl)oxadiazolyl)	94-96	44a	13
29a	*t*-Bu	5-(3-(2-furanyl)oxadiazolyl	157-159	44a	13
30a	*t*-Bu	5-(3-cyclopropyl)oxadiazolyl	176-178	44a	13
31a	NO_2	Br	187-189	31b	1
32a	*t*-Bu	4-morpholinyl	141-143	32b	1
33a	*t*-Bu	5-(3-methyl)oxadiazolyl	142-145	44a	13
34a	*i*-Pr	1-benzimidazolyl	150-152	34b	1
35a	*t*-Bu	1-(5-*t*-butyl)benzimidazolyl	263-265	35b	1
36a	NO_2	1-imidazolyl	232-234	31a	2
37a	*t*-Bu	CN	138-140	37b	1
38a	Ph	1-(2-methyl)imidazolyl	192-194	9b	1
39a	CF_3	1-benzimidazolyl	275-279	39b	1
40a*	CF_3	3-acetamino	223-226	40b	1
41a	HCONH	1-imidazolyl	234-235	41b	1[d]
42a	CF_3	1-(5-triflouromethyl)-benzimidazolyl	171-172	42b	1
43a	*t*-Bu	Br	132-134	43b	1
44a	*t*-Bu	COOH	215-216	44b	1
45a	3-furanyl	3-pyridyl	160-163	18a	11[b]
46a	Ph	3-pyridyl	139-141	18a	11[e]
47a	*i*-PrO_2C	Br	102-104	47b	1
48a	*i*-PrO_2C	3-pyridyl	108-111	47a	11[c]
49a	CH_2OH	3-pyridyl	183-185	48a	33
50a	CHO	3-pyridyl	200-202	49a	34
51a	3-pyridyl	3-pyridyl	178-182	18a	11[c]
52a	CHNOH	3-pyridyl	228-230	50a	35
53a	3-(3-cyclopropyl)oxadiazolyl	3-pyridyl	178-180	48a	13
54a	2-nitrophenyl	3-pyridyl	195-197	18a	11[f]
55a	$CHNNH_2$-$C(O)NH_2$	3-pyridyl	275-278	50a	36
56a	1-imidazolyl	3-pyridyl	187-190	18a	2
57a	2-furanyl	3-pyridyl	160-165	18a	2[g]
58a	CH_2OCH_3	3-pyridyl	119-120	66a	11[c]
59a	$CHNOCH_3$	3-pyridyl	205-207	50a	35[h]
60a*	*i*-Pr	3-pyridyl	155-160	61a	11[c]
61a	*i*-Pr	Br	82-86	61b	1

62a*	cyclopropyl-methyloxy	Br		160-168	63a	38[j]
63a	OH	Br		230-234	63b	1[j]
64a	benzyloxy	Br		189-193	63a	33[k]
65a	CH_2OH	Br		112-114	47a	33
66a	CH_2OCH_3	Br		**	65a	38

* isolated as the hydrochloride

**isolated as an oil

[a] decomp.

[b] Starting from 3-furanylboronic acid

[c] Starting from diethyl 3-pyridylborane

[d] The 5-amino group is formylated during the reaction

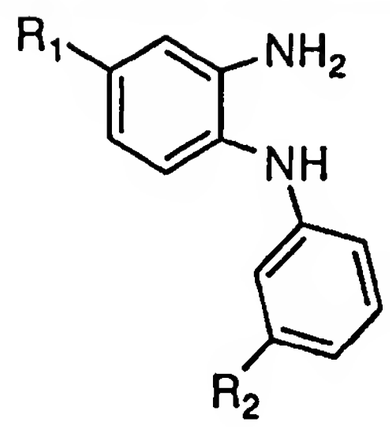
[e] Starting from phenylboronic acid

[f] Starting from 2-nitrophenylboronic acid

[g] Starting from 2-(tributylstannyl)furane

[h] Starting from methoxylamine hydrochloride

Table 2. Compounds 1b-63b.

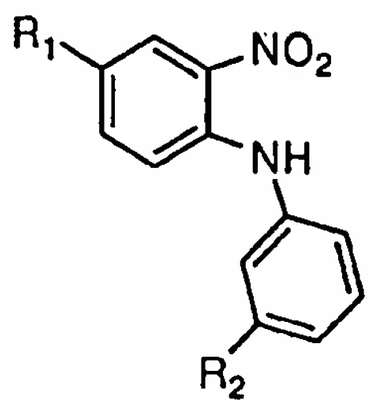


No	R_1	R_2	Mp/°C	Starting material	Example
1b*	CF_3	I	182-185	1c	3
2b	Me	CN	173-174	2c	3a
4b	*i*-PrO_2C	1-imidazolyl	**	4c	4a
5b	Me	1-imidazolyl	143-148	5c	3a
6b	*t*-Bu	1-imidazolyl	184-187	6c	3a
7b	*t*-Bu	1-(4-phenylimidazolyl)	**	7c	4a
8b	*t*-Bu	1-(4-methylimidazolyl)	**	8c	4a
9b	Ph	1-imidazolyl	210-215	9c	3a
10b	n-Bu	1-imidazolyl		10c	4
11b	n-Bu	1-(4-phenylimidazlolyl)		11c	4
12b	n-Bu	1-(2-methylimidazolyl)		12c	4
13b*	$(CH_2)_5CH$	1-imidazolyl	175-181	13c	4
14b*	*i*-Pr	1-imidazolyl	185-190	14c	4
15b*	*i*-Pr	1-(4-phenylimidazolyl)	265-268	15c	4
16b	*i*-Pr	1-(2-methylimidazolyl)		16c	4
31b	NO_2	Br	177-179	31d	3a
32b	*t*-Bu	4-morpholinyl	**	32c	3a
34b	*i*-Pr	1-benzimidazolyl	**	34c	4a
35b	*t*-Bu	(2-amino-4-*t*-butyl-phenyl)amino	222-224	35c	4a
37b*	*t*-Bu	CN	207-208	37c	4
39b	CF_3	(2-aminophenyl)amino	**	39c	4a
40b*	CF_3	acetamino	219-221	40c	4
41b*	NH_2	1-imidazolyl	258-262	41c	4
42b*	CF_3 amino	(2-amino-4-*t*-butylphenyl)-	170-173	42c	4
43b*	*t*-Bu	Br	213-215	43c	3
44b	*t*-Bu	COOH	158-160	44c	4a

47b	i-PrO_2C	Br		98-101	47d	3a
61b*	i-Pr	Br		197-203	14d	3
63b	cyclopro-pylmethoxy	Br		122-125	63c	3a

*isolated as the hydrochloride.
**isolated as an oil.

Table 3. Compounds 1c-63c.



No.	R_1	R_2	Mp/°C	Starting material	Example
1c	CF_3	I	98-101		5a
2c	Me	CN	162-163		2[b]
4c	*i*-PrO_2C	1-imidazolyl	**	4d	2
5c	Me	1-imidazolyl	124-126	5d	2
6c	*t*-Bu	1-imidazolyl	**	6d	2
7c	*t*-Bu	1-(4-phenylimidazolyl	**	6d	2
8c	*t*-Bu	1-(4-methylimidazolyl	**	6d	2
9c	Ph	1-imidazolyl	114-120	9d	2
10c	n-Bu	1-imidazolyl		10d	2
11c	n-Bu	1-(4-phenylimidazolyl)		10d	2
12c	n-Bu	1-(2-methylimidazolyl)		10d	2
13c	$(CH_2)_5CH$	1-imidazolyl	**	13d	2
14c	*i*-Pr	1-imidazolyl	65-66	14d	2
15c	*i*-Pr	1-(4-phenylimidazolyl)	123-124	14d	2
16c	*i*-Pr	1-(2-methylimidazolyl)		14d	2
32c	*t*-Bu	4-morpholinyl	**		14
34c	*i*-Pr	1-benzimidazolyl	**	14d	2
35c	*t*-Bu	(2-nitro-4-*t*-butylphenyl)-amino	120-122		6[c]
37c	*t*-Bu	CN	83-84		6[b]
39c	CF_3	(2-nitrophenyl)amino	95-98	45c	15
40c	CF_3	acetamino	188-190	45c	16
41c	NO_2	1-imidazolyl	167-169	31d	2
42c	CF_3	(2-nitro-4-triflouromethyl-phenyl)amino	133-135		15
43c	*t*-Bu	Br	74-76	6d	6

44c	*t*-Bu	COOH	194-195	17
45c	CF_3	NH_2	110-112	15
63c	cyclopropylmethoxy	Br	76-82	6[d]/38[e]

**isolated as an oil.

[a] commercial available starting materials are not listed.

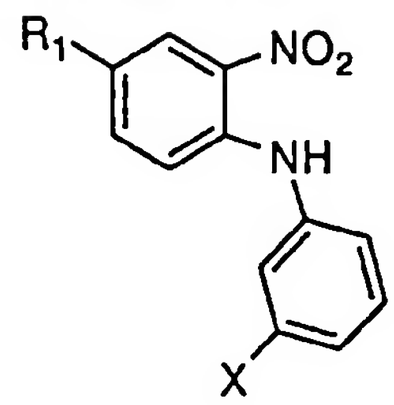
[b] starting from 4-methyl-2-nitroaniline and 3-bromobenzonitrile.

[c] 2 equivalents of 4-*t*-butyl-2-nitroaniline was used.

[d] using 1,3-dibromobenzene.

[e] using bromomethylcyclopropane.

Table 4. Compounds 4d-47d.



No.	R	X	Mp/°C	Example
4d	*i*-PrO_2C	I	176-179	5a[a]
5d	Me	Br	103-104	6
6d	*t*-Bu	Br	86-87	6/7
9d	Ph	Br	109-110	6/8
10d	n-Bu	Br	**	6/7
13d	$(CH_2)_5CH$	Br	**	6/7
14d	*i*-Pr	Br	51-52	6/7[b]
31d	NO_2	Br	170-172	5a[c]
47d	*i*-PrO_2C	Br	162-165	5a[d]

**isolated as an oil.

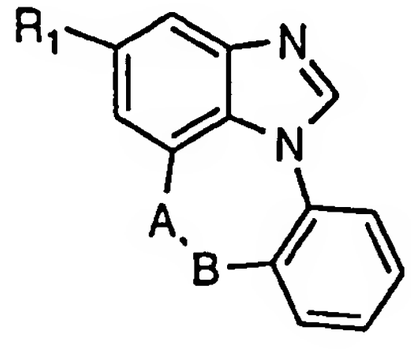
[a]starting from isopropyl 4-chloro-3-nitrobenzoate and 3-iodoaniline.

[b]a catalytic amount of conc. sulfuric acid was added to the acetanilide/acetic anhydride suspension prior to nitration.

[c]starting from 2,4-dinitrofluorobenzene and 3-bromaniline.

[d] starting from 2,4-dinitrofluorobenzene and 3-bromoaniline.

Table 5. Compounds 1f-8f.

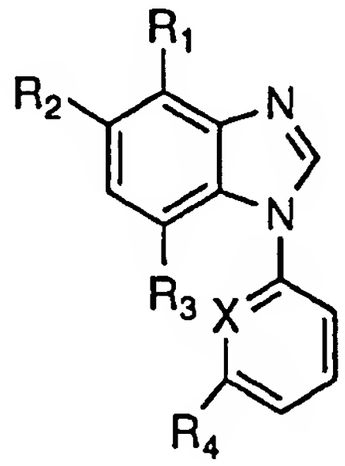


No.	A	B	R	Mp/°C	Starting material	Example
1f	NH	C=O	CF_3	330-332		22
2f	NMe	C=O	CF_3	197-198	1f	23
3f	NEt	C=O	CF_3	173-174	1f	23[a]
4f	NMe	CHOH	CF_3	169-170	2f	24
5f	N	CH	CF_3	242-243		25
6f	not present	C=O	Me	255-257		26
7f	not present	C=O	*t*-Bu	240-242		26[b]
8f	not present	CHOH	*t*-Bu	188-190	7f	24

[a] Using iodoethane instead of iodomethane.

[b] Starting from 4-*t*-butyl-2-nitroaniline. Example 7.

Table 6. Compounds 1g-15g.



No.	R_1	R_2	R_3	R_4	X	Mp/°C	Starting material	Ex.
1g	H	CF_3	3-pyridyl	H	CH	118-120	4g	11[a]
2g	H	CF_3	3-aminophenyl	H	CH	202-205	4g	11
3g	$COCH_3$	H	H	NO_2	CH	175-177		18
4g	H	CF_3	I	H	CH	118-120		9
5g	NO_2	H	H	3-pivaloylamino	CH	105-110		19
6g	H	*t*-Bu	H	Br	N	98-100		20
7g	NO_2	H	H	Br	CH	180-182		21
8g	H	CF_3	NH_2	Ph	CH	70-71	9g	4
9g	H	CF_3	NO_2	Ph	CH	150-152		9[b]
10g	H	CF_3	3-aminophenyl	CN	CH	211-215	11g	11
11g	H	CF_3	I	CN	CH	174-175		9[c]
12g	H	CF_3	Ph	H	CH	174-176	13g	11[d]
13g	H	CF_3	I	H	CH	118-120	14g	9[e]
14g*	H	CF_3	NH_2	H	CH	**		9[f]
15g	H	CF_3	PhCONH	H	CH	152-155	14g	37

* Isolated as the hydrochloride.

**Used without purification.

[a] Using diethyl 3-pyridylborane

[b] Analogueously to **4i** from 4-chloro-3,5-dinitrobenzoetrifluoride and 3-aminobiphenyl.

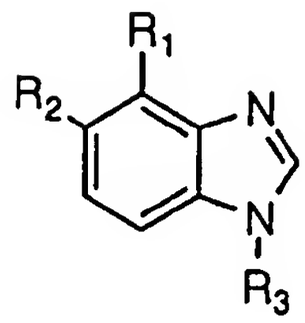
[c] Analogueously to **4g** from 4-chloro-3,5-dinitrobenzoetrifluoride and 3-aminobenzonitril.

[d] Using phenylboronic acid.

[e] Analogueously to **4g**.

[f] Analogueously to **4h** starting from 4-chloro-3,5-dinitrobenzoetrifluoride.

Table 7. Compounds 1k-11k.

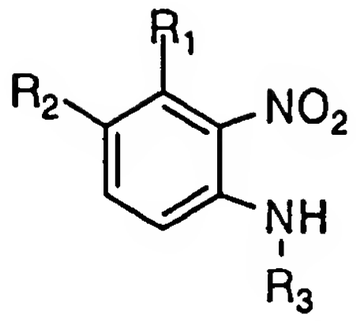


No.	R_1	R_2	R_3	Mp/°C	Starting material	Example
1k	=N-S-N=		3-iodophenyl	193-195	1l	1/3
2k	-CH=CH-CH=CH-		3-nitrophenyl	136-138	3k	31
3k	-CH=CH-CH=CH-		H	273-285	1,2-diamino-naphtalene	1/32
4k	-CH=CH-CH=N-		3-nitrophenyl	219-221	5k	31
5k	-CH=CH-CH=N-		H	270-272	5,6-diamino-** quinoline	1
6k*	$-CH_2-N(CH_3)-(CH_2)_2-$		3-nitrophenyl	266-269	7k	31
7k*	$-CH_2-N(CH_3)-(CH_2)_2-$		H	297-299	5,6-diamino-3-methyl-1,2,3,4-tetrahydroisoquinoline	32
8k*	H	*t*-Bu	8-isoquinolyl	253-260	8l	1/3
9k	H	CF_3	5-quinolyl	181-183	9l	1/4
10k	H	CF_3	6-quinolyl	190-194	10l	1/4
11k	H	CF_3	1-naphtyl	170-173	11l	1/3

* Isolated as the hydrochloride.

**Preparation as described in United States patent appln. Ser. No. 08/124,770 of Sept. 24, 1993

Table 8. Compounds 1l-11l.

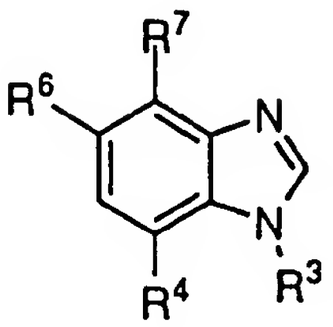


No.	R_1	R_2	R_3	Mp/°C	Starting material	Example
1l	=N-S-N=		3-iodophenyl	224-225	4-chloro-3-nitrobenzothiadiazole	5a
8l	H	CF_3	8-isoquinolyl	*	8-bromoisoquinoline	6
9l	H	CF_3	5-quinolyl	138-140	5-aminoquinoline	5a
10l	H	CF_3	6-quinolyl	158-160	6-aminoquinoline	5a
11l	H	CF_3	1-naphtyl	148-150	1-aminonaphtalene	5a

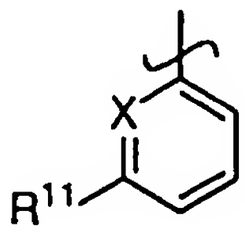
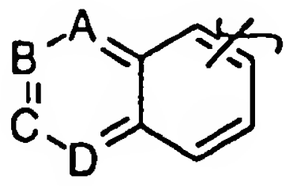
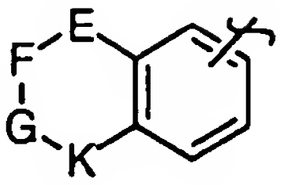
* Isolated as an oil.

Claims

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof
wherein
R^3 is


,  or 

wherein
X is N; or C-R' wherein R' is hydrogen or together with R^4 forms a $-(NR^{111})_m-C(=O)-$, $-(NR^{111})_m-$

CHOH-, or a -N=C- bridge wherein R^{111} is hydrogen or alkyl and m is 0 or 1;

one of A, B, C, and D is N and the others are CH;

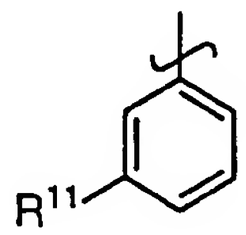
one of E, F, G, and K is N-R'' wherein R'' is hydrogen or alkyl and the others of E, F, G, and K are CH_2;

R^6 and R^7 are independently hydrogen; halogen; amino; nitro; cyano; acylamino; trifluoromethyl; alkyl; alkoxy; COO-alkyl; acyl; CH=NOH, CH=NO-alkyl; CH=N-NH-(C=O)-NH_2; phenyl which may be substituted one or more times with alkyl, nitro, halogen, or CF_3; or aryl which may be substituted one or more times with alkyl, phenyl, halogen, or CF_3; or R^6 and R^7 together forms a $(CH_2)_a$-$(Z)_b$-$(C=Y)_c$-$(Z')_d$-$(CH_2)_e$ bridge wherein each of Z and Z' independently are O, S, or NR''' wherein R''' is hydrogen or alkyl, Y is O or H_2, a and e are each independently 0, 1, 2, or 3 and b, c, and d are each independently 0 or 1 provided that the sum of a, b, c, d, and e is not larger than 6; or R^6 and R^7 together forms a -CH=CH-CH=N-, -CH=CH-N=CH-, -CH=N-CH=CH-, -N=CH-CH=CH-, or =N-S-N= bridge;

R^4 is hydrogen; amino; nitro; cyano; halogen; acylamino; phenyl which may be substituted one or more times with alkyl, amino, halogen, or CF_3; aryl which may be substituted one or more times with alkyl, phenyl, halogen, or CF_3; or R^4 together with R' forms a -$(NR^{111})_m$-C(=O)-, -$(NR^{111})_m$-CHOH-, or a -N=C- bridge wherein R^{111} is hydrogen or alkyl, and m is 1;

R^{11} is phenyl which may be substituted one or more times with alkyl, halogen, or CF_3; benzimidazolyl which may be substituted one or more times with alkyl, halogen, or CF_3; or aryl which may be substituted one or more times with alkyl, phenyl, halogen, or CF_3, amino, nitro, cyano, acylamino, trifluoromethyl; alkoxy; or acyl; provided that at least one of R^6 and R^7 is other than hydrogen.

2. A compound of claim 1 wherein R^4 is hydrogen and R^3 is

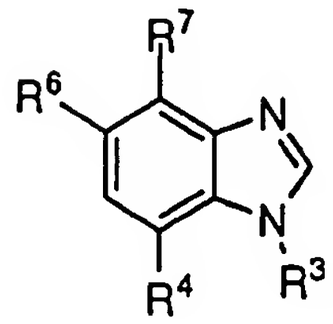


wherein R^{11} is pyridyl.

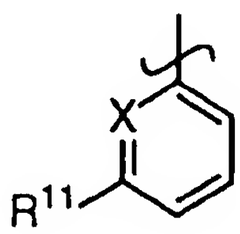
3. A compound of claim 1, which is
1-[3-(3-pyridyl)-phenyl]-5-methylaldoximo-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-*i*-propyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-(2-furanyl)-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-6-iodo-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-methyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-t-butyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-phenyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-*i*-propyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-iodo-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-*t*-butyl-benzimidazole,
1-[3-(1-benzimidazolyl)-phenyl]-5-i-propyl-benzimidazole,
1-[3-(1-(2-methylimidazolyl))-phenyl]-5-phenyl-benzimidazole,
1-[3-(1-benzimidazolyl)-phenyl]-5-trifluoromethyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-(3-furanyl)-benzimidazole, or
4-trifluoromethyl-6,7-dihydro-6-methyl-7-oxo-benzimidazo-[3,4-ab][1,4]benzodiazepine,
or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising an effective amount of a compound of claim 1, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent.

5. The use of a compound having the formula:



or a pharmaceutically acceptable salt thereof
wherein
R^3 is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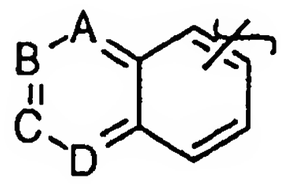
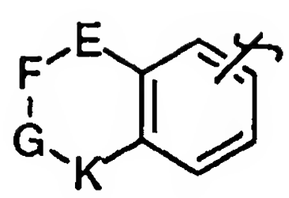

or


wherein
X is N; or C-R' wherein R' is hydrogen or together with R^4 forms a $-(NR^{111})_m-C(=O)-$, $-(NR^{111})_m-CHOH-$, or a -N=C- bridge wherein R^{111} is hydrogen or alkyl and m is 0 or 1;
one of A, B, C, and D is N and the others are CH;
one of E, F, G, and K is N-R'' wherein R'' is hydrogen or alkyl and the others of E, F, G, and K are CH_2;
R^6 and R^7 are independently hydrogen; halogen; amino; nitro; cyano; acylamino; trifluoromethyl; alkyl; alkoxy; COO-alkyl; acyl; CH=NOH, CH=NO-alkyl; $CH=N-NH-(C=O)-NH_2$; phenyl which may be substituted one or more times with alkyl, nitro, halogen, or CF_3; or aryl which may be substituted one or more times with alkyl, phenyl, halogen, or CF_3; or R^6 and R^7 together forms a $(CH_2)_a-(Z)_b-(C=Y)_c-(Z')_d-(CH_2)_e$ bridge wherein each of Z and Z' independently are O, S, or NR''' wherein R''' is hydrogen or alkyl, Y is O or H_2, a and e are each independently 0, 1, 2, or 3 and b, c, and d are each independently 0 or 1 provided that the sum of a, b, c, d, and e is not larger than 6; or R^6 and R^7 together forms a -CH=CH-CH=N-, -CH=CH-N=CH-, -CH=N-CH=CH-, -N=CH-CH=CH-, or =N-S-N= bridge;
R^4 is hydrogen; amino; nitro; cyano; halogen; acylamino; phenyl which may be substituted one or more times with alkyl, amino, halogen, or CF_3; aryl which may be substituted one or more times with alkyl, phenyl, halogen, or CF_3; or R^4 together with R' forms a $-(NR^{111})_m-C(=O)-$, $-(NR^{111})_m-CHOH-$, or a -N=C- bridge wherein R^{111} is hydrogen or alkyl, and m is 1;
R^{11} is halogen; amino; nitro; cyano; COO-alkyl; acylamino; CF_3; alkyl; alkoxy; morpholinyl; phenyl which may be substituted one or more times with alkyl, halogen, or CF_3; benzimidazolyl which may be substituted one or more times with alkyl, halogen, or CF_3; or aryl which may be substituted one or more times with alkyl, phenyl, halogen, or CF_3, amino, nitro, cyano, acylamino, trifluoromethyl; alkoxy; or acyl, for the manufacture of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which is responsive to modulation of the benzodiazepine receptor of the central nervous system of such a living animal body, including a human.

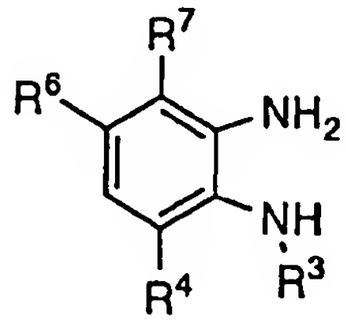
6. The use of a compound of claim 2 for the manufacture of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which is responsive to modulation of the benzodiazepine receptor of the central nervous system of such a living animal body, including a human.

7. The use of a compound as in claim 5 for the manufacture of a medicament for the treatment of anxiety, sleep disorders, memory disorders, epilepsy or any other convulsive disorder of a living animal body, including a human.

8. The use as in claim 5, wherein the compound employed is
1-[3-(3-pyridyl)-phenyl]-5-methylaldoximo-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-*i*-propyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-(2-furanyl)-benzimidazole,

1-[3-(3-pyridyl)-phenyl]-6-iodo-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-methyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-t-butyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-phenyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-*i*-propyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-iodo-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-*t*-butyl-benzimidazole,
1-[3-(1-benzimidazolyl)-phenyl]-5-i-propyl-benzimidazole,
1-[3-(1-(2-methylimidazolyl))-phenyl]-5-phenyl-benzimidazole,
1-[3-(1-benzimidazolyl)-phenyl]-5-trifluoromethyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-(3-furanyl)-benzimidazole, or
4-trifluoromethyl-6,7-dihydro-6-methyl-7-oxo-benzimidazo-[3,4-ab][1,4]benzodiazepine,
or a pharmaceutically-acceptable addition salt thereof.

9. A method of preparing a compound of claim 1, comprising the step of reacting a compound having the formula



wherein R^3, R^4, R^6 and R^7 have the meanings set forth in claim 1, with formic acid or a reactive derivative thereof.

10. A method of claim 9 wherein
1-[3-(3-pyridyl)-phenyl]-5-methylaldoximo-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-*i*-propyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-(2-furanyl)-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-6-iodo-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-methyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-t-butyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-phenyl-benzimidazole,
1-[3-(1-imidazolyl)-phenyl]-5-*i*-propyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-iodo-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-*t*-butyl-benzimidazole,
1-[3-(1-benzimidazolyl)-phenyl]-5-i-propyl-benzimidazole,
1-[3-(1-(2-methylimidazolyl))-phenyl]-5-phenyl-benzimidazole,
1-[3-(1-benzimidazolyl)-phenyl}-5-trifluoromethyl-benzimidazole,
1-[3-(3-pyridyl)-phenyl]-5-(3-furanyl)-benzimidazole, or
4-trifluoromethyl-6,7-dihydro-6-methyl-7-oxo-benzimidazo-[3,4-ab][1,4]benzodiazepine,
or a pharmaceutically-acceptable addition salt thereof, is prepared.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 94 61 0012

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
P,X	EP-A-0 563 001 (NEUROSEARCH A/S) 29 September 1993 * the whole document * ---	1-10	A61K31/415 A61K31/44 C07D401/10 C07D405/14 C07D403/10 C07D235/06 C07D487/06 C07D471/06 C07D405/00 C07D413/00 C07D401/00 C07D513/04
A	EP-A-0 520 200 (NEUROSEARCH A/S) * the whole document * ---	1-10	
A	US-A-5 158 969 (S.-P. OLESEN ET AL.) * the whole document * ---	1-10	
X	CHEMICAL ABSTRACTS, vol. 100, no. 17, 23 April 1984, Columbus, Ohio, US; abstract no. 139029t, F.A. HUSSEIN ET AL '1-(Para or meta-cinnamoylphenyl)-5-nitrobenzimidazoles' page 644 ; * abstract * * see also attached computer print-out * & IRAQI J. SCI. vol. 23, no. 3 , 1982 pages 293 - 309 --- -/--	1,9,10	

TECHNICAL FIELDS SEARCHED (Int.Cl.5)

C07D
A61K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims
Claims searched completely :
Claims searched incompletely :
Claims not searched :
Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	27 June 1994	Allard, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
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L : document cited for other reasons

& : member of the same patent family, corresponding document

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Application Number
EP 94 61 0012

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	TETRAHEDRON vol. 31 , September 1975 , OXFORD GB pages 2163 - 2170 K.T. POTTS ET AL. 'Aromatic substitution by N-arylhydroxylamines-I' * page 2166, formula 16 * -----	1,9,10	
			TECHNICAL FIELDS SEARCHED (Int.Cl.5)

EPO FORM 1503 03.82 (P04C10)

EP 94 61 0012

-C-

INCOMPLETE SEARCH

Claims searched completely: 2,3,6,8,10

Claims searched incompletely: 1,4,5,7,9

An exhaustive search for claims 1,4,5,7 and 9 would have to cover such a large number of subdivisions of the systematically arranged documentation that such search would not be economically justified. The search has consequently been limited to the subdivisions of the documentation which are supported by examples in the description, see Guidelines for Examination in the EPO, B-III,2.1 and 3.7.

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(71) Applicant *(for all designated States except US)*: **NEUROSEARCH A/S** [DK/DK]; Pederstrupvej 93, DK-2750 Ballerup (DK).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **TEUBER, Lene** [DK/DK]; c/o NeuroSearch A/S, Pederstrupvej 93, DK-2750 Ballerup (DK). **WÄTJEN, Frank** [DK/DK]; c/o NeuroSearch A/S, Pederstrupvej 93, DK-2750 Ballerup (DK).

(74) Common Representative: **NEUROSEARCH A/S**; Patent Department, Pederstrupvej 93, DK-2750 Ballerup (DK).

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WO 00/78728 A1

(54) Title: NOVEL BENZIMIDAZOLE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS COMPRISING THESE COMPOUNDS

(57) Abstract: The present invention relates to novel benzimidazole derivatives, pharmaceutical compositions containing these compounds, and methods of treatment therewith. The compounds of the invention are useful in the treatment of central nervous system diseases and disorders, which are responsive to modulation of the GABA^ receptor complex, and in particular for inducing and maintaining anaesthesia, sedation and muscle relaxation, as well as for combating febrile convulsions in children. The compounds of the invention may also be used by veterinarians.

NOVEL BENZIMIDAZOLE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS COMPRISING THESE COMPOUNDS

TECHNICAL FIELD

The present invention relates to novel benzimidazole derivatives, pharmaceutical compositions containing these compounds, and methods of treatment therewith.

The compounds of the invention are useful in the treatment of central nervous system diseases and disorders, which are responsive to modulation of the $GABA_A$ receptor complex, and in particular for inducing and maintaining anaesthesia, sedation and muscle relaxation, as well as for combating febrile convulsions in children.

The compounds of the invention may also be used by veterinarians.

BACKGROUND ART

Agents that bind or interact with the modulatory sites on the $GABA_A$ receptor complex, such as for example the benzodiazepine receptor, can have either enhancing effect on the action of GABA, i.e. a positive modulatory effect of the receptor (agonists, partial agonists), an attenuating effect on the action of GABA, i.e. negative modulation of the receptor (inverse agonists, partial inverse agonists), or they can block the effect of both agonists and inverse agonists (antagonists or ligands without intrinsic activity).

Agonists generally produce muscle relaxant, hypnotic, sedative, anxiolytic, and/or anticonvulsant effects, while inverse agonists produce pro-convulsive, anti-inebriant or anxiogenic effects. Compounds with anxiolytic effects, but with or without reduced muscle relaxant, hypnotic and sedative effects, are characterised as partial agonists. Partial inverse agonists are considered to be useful as cognition enhancers.

Full agonists of the benzodiazepine receptor are considered useful as anaesthetics. However, many drugs presently available as anaesthetics, and especially pre-anaesthetics, give rise to hang-over effects as well as long awakening times, wherein careful monitoring of the patient is necessary. Anaesthetics with a long half-life may also impose difficulties during incidents of overdosing i.e. prolonged respiratory depression. Furthermore, some currently used drugs cannot be used for anaesthetising children as deaths have been reported in children after prolonged use of Propofol. Some anaesthetics are gasses which inherently possesses a contamination problem for the medical staff.

A well known anaesthetic, Propofol, is administered as a mixture of soybean oil, glycerol and purified egg phosphatide, which mixture nourish bacterial growth. Administration of bacterially contaminated Propofol has been reported to cause sepsis and death [*Wiklund et al.*; The New England Journal of Medicine 1997 **337** (16) 1132-1141]. Further, compounds with a long *in vivo* half-life will give problems with accumulation during and after prolonged treatment e.g. when administered to patients constrained to a respirator. Short half-lives wherein the compounds are metabolised to inactive metabolites allow for a predictable correlation of dose and duration of pharmacological effect.

Ideally the anaesthestising effect should be observed shortly after a bolus injection or infusion of the compound. A rapid onset of action minimises the period of anxiety and uneasiness experienced by patients going into surgery.

Patients suffering from severe and continuous epileptic attacks presently treated with large amounts of sedatives, e.g. benzodiazepines, will benefit from shorter acting compounds with no hang-over or long lasting sedating effect.

As the preferred route of administration is by intravenous injection or infusion, the anaesthestising compounds should preferably be water soluble.

EP 616807 describes benzimidazole compounds for use as benzodiazepine receptor ligands.

WO 96/33194, WO 96/33191 and WO 96/33192 describe benzimidazole compounds having affinity for the GABA receptor complex.

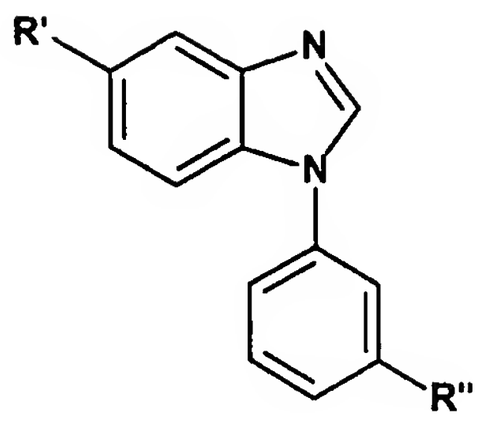
WO 98/34923 describes phenylbenzimidazole derivatives as ligands for the GABA receptor complex.

WO 98/17651 describes benzimidazole compounds for use as e.g. anaesthetics. However, the presently disclosed compounds are superior to the compounds previously described.

SUMMARY OF THE INVENTION

It is an object of the invention to provide novel compounds useful as anaesthetics and/or pre-anaesthetics, sedatives, muscle relaxants, and for the treatment of febrile convulsions in children, status epilepticus, for use to patients constrained to a respirator as well as for veterinarian uses.

In its first aspect, the invention provides a benzimidazole derivative represented by the general Formula I,



(I)

or a pharmaceutically acceptable salt thereof,

wherein,

R' represents a group of the formula $-(alk)_q-R^1$,

wherein

(alk) represents alkyl, alkenyl or alkynyl,

q is 0 or 1,

R^1 represents a group of the formula $-CO_2R^2$, wherein

R^2 represents hydrogen, alkyl, hydroxy-alkyl, alkoxy-alkyl, thioalkoxy-alkyl, alkyl-"Heterocycle", or $-alkyl-NR^3R^4$,

wherein

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, and a group of the formula $-(alkyl)_p-CN$, $-(alkyl)_p-aryl$, $-(alkyl)_p-$"Heterocycle", $-(alkyl)_p-CO_2-$"Heterocycle" or $-(alkyl-CO_2)_s-(alkyl)_t-COR^5$,

in which formulas

p, s and t independently of each another is 0 or 1,

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl,

R^5 represents hydroxy, alkoxy, hydroxy-alkoxy, alkoxy-alkoxy, thioalkoxy-alkoxy, or a group of the formula $-NR^6R^7$ or $-O-alkyl-NR^6R^7$,

in which formulas

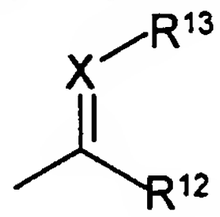
R^6 and R^7 independently of each another represent hydrogen, alkyl, cycloalkyl or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, or

R^6 and R^7 together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group may be substituted

one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl; and

R^3 and R^4 independently of each another represent hydrogen, alkyl or cycloalkyl, or

R^3 and R^4 together with the nitrogen to which they are attached form a mono- or poly-cyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl; or

R^1 represents a group of the formula  , wherein

X represents N or CH,

R^{12} represents hydrogen, alkyl, alkoxy or hydroxy-alkyl, and

R^{13} represents hydrogen, hydroxy, alkyl, alkoxy or hydroxy-alkyl; or

R^1 represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, hydroxy-alkyl, alkoxy-alkyl, carboxyl, and acyl, and a group of the formula $-(alkyl)_p$-aryl, $-(alkyl)_p$-"Heterocycle", $-(alkyl)_p$-CN or $-(alkyl\text{-}CO_2)_s$-$(alkyl)_t$-COR^5,

in which formulas

p, s and t independently of each another is 0 or 1,

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl,

R^5 represents hydroxy, alkoxy, hydroxy-alkoxy, alkoxy-alkoxy, thioalkoxy-alkoxy, or a group of the formula $-NR^6R^7$ or -O-alkyl-NR^6R^7,

in which formulas

R^6 and R^7 independently of each another represent hydrogen, alkyl, cycloalkyl or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, or

R^6 and R^7 together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl; and

R'' represents $-(alkyl)_o$-"Heterocycle" or $-(alkyl)_o$-CO_2-$(alkyl)_u$-"Heterocycle",

wherein

o and u independently of each another is 0 or 1, and

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl, and acyl, and a group of the formula $-(alkyl)_p-CN$, $-(alkyl)_p-aryl$, $-(alkyl)_p-aralkyl$, $-(alkyl)_p-O-aryl$, $-(alkyl)_p-O-aralkyl$, $-(alkyl)_p-CO_2-aryl$, $-(alkyl)_p-CO_2-aralkyl$, $-(alkyl)_p-$"Heterocycle", $-(alkyl)_p-CO_2-$"Heterocycle" or $-(alkyl-CO_2)_s-(alkyl)_t-COR^5$,

in which formulas

p, s and t independently of each another is 0 or 1,

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl,

R^5 represents hydrogen, hydroxy, alkyl, alkoxy, hydroxy-alkyl, hydroxy-alkoxy, alkoxy-alkyl, alkoxy-alkoxy, thioalkoxy-alkyl, thioalkoxy-alkoxy, or a group of the formula $-NR^6R^7$ or $-O-alkyl-NR^6R^7$,

in which formulas

R^6 and R^7 independently of each another represent hydrogen, alkyl, cycloalkyl or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, or

R^6 and R^7 together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl; or

R'' represents $-(alkyl)_m-CO_2R^8$,

wherein

m is 0 or 1, and

R^8 represents hydrogen, alkyl, hydroxy-alkyl, alkoxy-alkyl, thioalkoxy-alkyl, or a group of the formula $-(alkyl)_p-NR^9R^{10}$,

wherein

p is 0 or 1, and

R^9 and R^{10} independently of each another represent hydrogen, alkyl, cycloalkyl, or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group

consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, or

R^9 and R^{10} together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl.

In its second aspect, the invention provides a pharmaceutical composition containing a therapeutically effective amount of a benzimidazole derivative according to the invention, or a pharmaceutically acceptable addition salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In its third aspect, the invention provides a use of a benzimidazole derivative according to the invention for the manufacture of a medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of the GABA receptor complex.

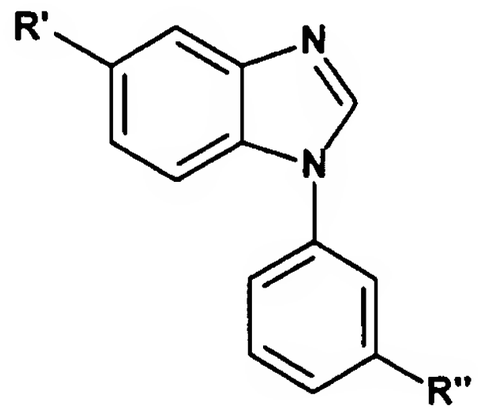
In its fourth aspect, the invention provides a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of the GABA receptor complex, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a benzimidazole derivative according to the invention.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and the working examples.

DETAILED DISCLOSURE OF THE INVENTION

Benzimidazole Derivatives

In its first aspect the invention provides novel benzimidazole derivatives. The benzimidazole derivatives of the invention are represented by the general Formula I,



(I)

or a pharmaceutically acceptable salt thereof,

wherein,

R' represents a group of the formula -$(alk)_q$-R^1,

wherein

(alk) represents alkyl, alkenyl or alkynyl,

q is 0 or 1,

R^1 represents a group of the formula -CO_2R^2, wherein

R^2 represents hydrogen, alkyl, hydroxy-alkyl, alkoxy-alkyl, thioalkoxy-alkyl, alkyl-"Heterocycle", or -alkyl-NR^3R^4,

wherein

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, and a group of the formula -$(alkyl)_p$-CN, -$(alkyl)_p$-aryl, -$(alkyl)_p$-"Heterocycle", -$(alkyl)_p$-CO_2-"Heterocycle" or -$(alkyl\text{-}CO_2)_s$-$(alkyl)_t$-COR^5,

in which formulas

p, s and t independently of each another is 0 or 1,

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl,

R^5 represents hydroxy, alkoxy, hydroxy-alkoxy, alkoxy-alkoxy, thioalkoxy-alkoxy, or a group of the formula -NR^6R^7 or -O-alkyl-NR^6R^7,

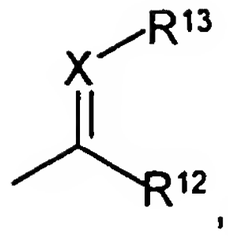
in which formulas

R^6 and R^7 independently of each another represent hydrogen, alkyl, cycloalkyl or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, or

R^6 and R^7 together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group may be substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl; and

R^3 and R^4 independently of each another represent hydrogen, alkyl or cycloalkyl, or

R^3 and R^4 together with the nitrogen to which they are attached form a mono- or poly-cyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl; or

R^1 represents a group of the formula  , wherein

X represents N or CH,

R^{12} represents hydrogen, alkyl, alkoxy or hydroxy-alkyl, and

R^{13} represents hydrogen, hydroxy, alkyl, alkoxy or hydroxy-alkyl; or

R^1 represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, hydroxy-alkyl, alkoxy-alkyl, carboxyl, and acyl, and a group of the formula $-(alkyl)_p$-aryl, $-(alkyl)_p$-"Heterocycle", $-(alkyl)_p$-CN or $-(alkyl\text{-}CO_2)_s$-$(alkyl)_t$-COR^5,

in which formulas

p, s and t independently of each another is 0 or 1,

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl,

R^5 represents hydroxy, alkoxy, hydroxy-alkoxy, alkoxy-alkoxy, thioalkoxy-alkoxy, or a group of the formula $-NR^6R^7$ or $-O\text{-}alkyl\text{-}NR^6R^7$,

in which formulas

R^6 and R^7 independently of each another represent hydrogen, alkyl, cycloalkyl or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, or

R^6 and R^7 together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl; and

R'' represents $-(alkyl)_o$-"Heterocycle" or $-(alkyl)_o\text{-}CO_2\text{-}(alkyl)_u$-"Heterocycle",

wherein

o and u independently of each another is 0 or 1, and

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl, and acyl, and a group of the formula $-(alkyl)_p$-CN, $-(alkyl)_p$-aryl, $-(alkyl)_p$-aralkyl, $-(alkyl)_p$-O-aryl, $-(alkyl)_p$-O-aralkyl, $-(alkyl)_p\text{-}CO_2$-aryl, $-(alkyl)_p$-

CO_2-aralkyl, -(alkyl)$_p$-"Heterocycle", -(alkyl)$_p$-CO_2-"Heterocycle" or -(alkyl-CO_2)$_s$-(alkyl)$_t$-COR^5,

in which formulas

p, s and t independently of each another is 0 or 1,

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl,

R^5 represents hydrogen, hydroxy, alkyl, alkoxy, hydroxy-alkyl, hydroxy-alkoxy, alkoxy-alkyl, alkoxy-alkoxy, thioalkoxy-alkyl, thioalkoxy-alkoxy, or a group of the formula -NR^6R^7 or -O-alkyl-NR^6R^7,

in which formulas

R^6 and R^7 independently of each another represent hydrogen, alkyl, cycloalkyl or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, or

R^6 and R^7 together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl; or

R'' represents -(alkyl)$_m$-CO_2R^8,

wherein

m is 0 or 1, and

R^8 represents hydrogen, alkyl, hydroxy-alkyl, alkoxy-alkyl, thioalkoxy-alkyl, or a group of the formula -(alkyl)$_p$-NR^9R^{10},

wherein

p is 0 or 1, and

R^9 and R^{10} independently of each another represent hydrogen, alkyl, cycloalkyl, or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, or

R^9 and R^{10} together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl.

In a preferred embodiment the benzimidazole derivative of the invention is represented by Formula I, wherein R'' represents

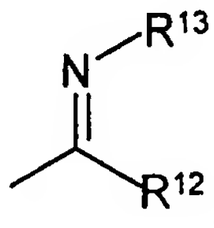
2-(4-acetylpiperazin-1-yl)-ethoxy-carbonyl;
pyridin-2-yl-methoxy-carbonyl;
1-Methyl-2-pyrrolidyl-methoxy-carbonyl; or
3,5-dimethyl-1-piperazinyl-ethoxy-carbonyl.

In a most preferred embodiment, the benzimidazole derivative is
2-(1-Acetyl-4-piperazinyl)-ethyl 3-(5-(3-furanyl)-1-benzimidazolyl)-benzoate;
1-Methyl-2-pyrrolidylmethyl 3-(5-(3-furanyl)-1-benzimidazolyl)-benzoate;
or a pharmaceutically acceptable salt thereof.

In another preferred embodiment the benzimidazole derivative of the invention is a compound of Formula I, wherein

R^1 represents a group of the formula $-CO_2R^2$, wherein

R^2 represents alkyl, hydroxy-alkyl, alkoxy-alkyl, thioalkoxy-alkyl, alkyl-$N(alkyl)_2$; or

R^1 represents a group of the formula  , wherein

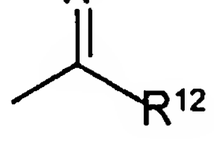
R^{12} represents alkyl, and

R^{13} represents hydroxy, or alkoxy; or

R^1 represents a furanyl group, a pyrazolyl group, an isoxazolyl group, an oxazolyl group, an oxadiazolyl group.

In a more preferred embodiment

R^1 represents a group of the formula -COOH, $-CO_2-CH_3$, $-CO_2-C_2H_5$, $-CO_2-CH_2-CH(OH)$, $-CO_2(CH_2)_2OCH_3$, $-CO_2(CH_2)_2SCH_3$, $-CO_2(CH_2)_2SC_2H_5$, or $-CO_2(CH_2)_2N(CH_3)_2$; or

R^1 represents a group of the formula  , wherein

R^{12} represents methyl or ethyl, and

R^{13} represents hydroxy, methoxy or ethoxy; or

R^1 represents a 2- or 3-furanyl group.

In a most preferred embodiment, the benzimidazole derivative is
2-(3,5-dimethyl-1-piperazinyl)-ethyl 3-(5-acetylbenzimidazol-1-yl)-benzoate oxime; or
2-(2-pyridyl)-methyl 3-(5-acetylbenzimidazol-1-yl)-benzoate oxime;
or a pharmaceutically acceptable salt thereof.

In another preferred embodiment the benzimidazole derivative of the invention is represented by Formula I, wherein

R'' represents a group of the formula -(alkyl)$_o$-"Heterocycle", wherein

o is 0 or 1, and

"Heterocycle" represents a furanyl group, a 2H-furanyl group, a 4H-furanyl group, a thienyl group, a pyrrolyl group, a 2H-pyrrolyl (pyrrolinyl) group, a 4H-pyrrolyl (pyrrolidinyl) group, an imidazolyl group, an oxazolyl group, a 2H-oxazolyl (oxazolinyl) group, a 4H-oxazolyl (oxazolidinyl) group, an isoxazolyl group, a 2H-isoxazolyl (isoxazolinyl) group, a 4H-isoxazolyl (isoxazolidinyl) group, an oxadiazolyl group, a 2H-oxadiazolyl (oxadiazolinyl) group, a 4H-oxadiazolyl (oxadiazolidinyl) group, a morpholinyl group, a thiomorpholinyl group, a pyridinyl group, a piperidinyl group, a piperazine group, a homopiperazine group or a tetrazolyl group, which heterocyclic groups may be substituted one or more times with substituents selected from the group consisting of halogen, alkyl, oxo, acyl, alkyl-CO_2H, alkyl-CO_2-alkyl -(alkyl)$_p$-CO_2-aryl, -(alkyl)$_p$-CO_2-aralkyl and alkyl-CO_2-alkyl-$CONR^6R^7$, wherein

R^6 and R^7 independently of each another represent hydrogen or alkyl.

In a more preferred embodiment,

"Heterocycle" represents a pyrrolidin-1-yl; a piperazin-1-yl; a homopiperazin-1-yl; an imidazol-1-yl; a pyridin-4-yl; a 4H-pyridin-4-yl, in particular a 1,2,5,6-tetrahydro-pyridin-4-yl; a piperidin4-yl; a 2H-isoxazol-3-yl, in particular a 4,5-dihydro-isoxazol-3-yl.

In a further preferred embodiment the benzimidazole derivative of the invention is represented by Formula I, wherein R''

4-ethoxycarbonyl-1-imidazolyl;

4-methoxycarbonyl-1-imidazolyl;

5-((N,N-Diethylcarbamoyl)-methoxy-carbonyl-methyl)-4,5-dihydroisoxazol-3-yl;

5-((N,N-Dimethylcarbamoyl)-methoxy-carbonyl-methyl)-4,5-dihydroisoxazol-3-yl;

1-imidazolylmethyl;

4-(1-methyl-5-tetrazolyl)-methyl-1-piperazinyl;

1-ethyl-1,2,5,6-tetrahydropyridin-4-yl;

4-(2-oxazolidinone-5-yl)-methyl)1-piperazinyl;

4-(5-methyloxadiazol-3-yl)-methyl)1-piperazinyl;

4-(3,5-dimethylisoxazol-4-yl)-methyl)1-piperazinyl;

4-(2-oxo-tetrahydrofuran-3-yl)-1-piperazinyl;

4-(2-chloro-5-thienyl)-methyl-1-piperazinyl; or

(1-methyl-2-pyrrolidyl)-methyl-carbonyl.

In a most preferred embodiment the benzimidazole derivative of the invention is

2-Methoxyethyl 1-(3-(4-methoxycarbonyl-1-imidazolyl)-phenyl)-benzimidazole-5-carboxylate;

(N,N-Diethylcarbamoyl)-methyl 2-(3-[3-(5-ethoxycarbonyl-1-benzimidazolyl)-phenyl]-4,5-dihydroxyisoxazol-5-yl)-acetate;

Methyl 1-(3-(1-imidazolylmethyl)-phenyl)-benzimidazole-5-carboxylate;

2-(Methylthio)-ethyl 1-(3-(1-imidazolylmethyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(1-methyl-5-tetrazolyl)methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(1-ethyl-1,2,5,6-tetrahydropyridin-4-yl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(2-oxazolidinone-5-yl)-methyl)1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(5-methyloxadiazol-3-yl)-methyl)1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(3,5-dimethylisoxazol-4-yl)methyl)1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(2-oxo-tetrahydrofuran-3-yl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(2-chloro-5-thienyl)-methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

5-(3-Furanyl)-1-(3-(4-methoxycarbonyl-1-imidazolyl)-phenyl)-benzimidazole;

or

N,N-Diethylcarbamoylmethyl 2-(3-(3-(5-(3-furanyl)-1-benzimidazolyl)-phenyl)-4,5-dihydroisoxazole-5-yl)-acetate;

or a pharmaceutically acceptable salt thereof.

In another preferred embodiment the benzimidazole derivative of the invention is represented by Formula I wherein

R'' represents a group of the formula $-CO_2-(alkyl)_o$-"Heterocycle", wherein

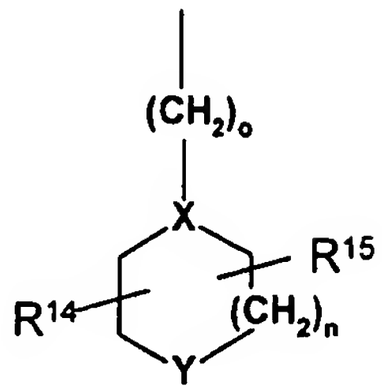
o is 0 or 1, and

"Heterocycle" represents a pyrrolyl group, a 2H-pyrrolyl (pyrrolinyl) group, a 4H-pyrrolyl (pyrrolidinyl) group, an imidazolyl group, an oxazolyl group, an isoxazolyl group, a 2H-isoxazolyl (isoxazolinyl) group, a 4H-isoxazolyl (isoxazolidinyl) group, an oxadiazolyl group, a pyridyl group, a piperidinyl group, a piperazine group or a homopiperazine group, which heterocyclic groups may be substituted one or more times with substituents selected from the group consisting of alkyl, acyl, alkyl-CO_2H, alkyl-CO_2-alkyl and alkyl-CO_2-alkyl-$CONR^6R^7$, wherein

R^6 and R^7 independently of each another represent hydrogen or alkyl.

In a more preferred embodiment the benzimidazole derivative of the invention is represented by Formula I, wherein

R'' represents a group of the formula



in which formula

o is 0 or 1,

n is 0, 1 or 2,

X represents N or CH,

Y represents O, NR^{11} or CHR^{11},

wherein R^{11} represents hydrogen, alkyl, hydroxy-alkyl, alkoxy-alkyl, carboxyl or acyl, or a group of the formula -$(alkyl)_p$-CN, -$(alkyl)_p$-aryl, -$(alkyl)_p$-O-aryl, -$(alkyl)_p$-O-aralkyl, -$(alkyl)_p$-"Heterocycle", -$(alkyl)_p$-CO_2-"Heterocycle" or -$(alkyl\text{-}CO_2)_s$-$(alkyl)_t$-COR^5,

wherein

p, s and t independently of each another is 0 or 1,

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl,

R^5 represents hydroxy, alkoxy, hydroxy-alkoxy, alkoxy-alkoxy, thioalkoxy-alkoxy, aryl or aralkyl, or a group of the formula -NR^6R^7 or -O-alkyl-NR^6R^7, in which formulas

R^6 and R^7 independently of each another represents hydrogen, alkyl, cycloalkyl or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, and acyl, or

R^6 and R^7 together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group may be substituted one or more times with substituents selected from the group consisting of alkyl and acyl, and

R^{14} and R^{15} independently of each another represent hydrogen, alkyl, hydroxy-alkyl, alkoxy-alkyl, carboxyl or acyl; or

R'' represents a group of the formula -CO_2R^8, wherein

R^8 represents alkyl-NR^9R^{10}, wherein

R^9 and R^{10} together with the nitrogen to which they are attached form a pyrrolidine or a piperazine group, which group may be substituted one or more times with substituents selected from the group consisting of alkyl and acyl.

In an even more preferred embodiment the benzimidazole derivative of the invention is represented by Formula I, wherein R'' represents

4-methoxycarbonyl-methyl-3,5-dimethyl-1-piperazinyl;

4-ethoxycarbonyl-methyl-3,5-dimethyl-1-piperazinyl;

4-methyl-3,5-dimethyl-1-piperazinyl;

4-ethyl-3,5-dimethyl-1-piperazinyl; or

3,5-dimethyl-1-piperazinyl.

In a most preferred embodiment the benzimidazole derivative of the invention is

2-Methoxyethyl 1-(3-(4-ethoxycarbonylmethyl-3,5-dimethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methyl 1-(3-(4-ethoxycarbonylmethyl-3,5-dimethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-ethyl-3,5-dimethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

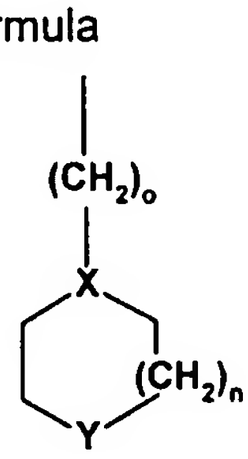
2-Methoxyethyl 1-(3-(3,5-dimethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate; or

2-(3,5-dimethyl-1-piperazinyl)-ethyl 3-(5-acetylbenzimidazol-1-yl)-benzoate oxime;

or a pharmaceutically acceptable salt thereof.

In yet another preferred embodiment the benzimidazole derivative of the invention is represented by Formula I wherein

R'' represents a group of the formula



in which formula

o is 0 or 1,

n is 0, 1 or 2,

X represents N or CH, and

Y represents NR^{11} or CHR^{11}, wherein

R^{11} represents hydrogen, alkyl, hydroxy-alkyl, carboxy, acyl, or a group of the formula -(alkyl)$_p$-CN, -(alkyl)$_p$-aryl, -(alkyl)$_p$-O-aryl, -(alkyl)$_p$-O-aralkyl, -(alkyl)$_t$-COR^5 or -(alkyl)$_t$-R^5,

wherein

p and t independently of each another is 0 or 1, and

R^5 represents hydroxy, alkoxy, NH_2, NH(alkyl) or N(alkyl)$_2$.

In a more preferred embodiment,

R'' represents

4-(methoxy-carbonyl)-1-piperazinylmethyl;

4-(ethoxy-carbonyl)-1-piperazinylmethyl;

4-(methoxy-carbonyl-methyl)-1-piperazinyl;

4-(ethoxy-carbonyl-methyl)-1-piperazinyl;

4-(methoxy-carbonyl-methyl)-1-piperazinylmethyl;

4-(ethoxy-carbonyl-methyl)-1-piperazinylmethyl;

1-piperazinyl;

1-piperazinyl-methyl;

4-acetyl-1-piperazinyl;

4-methyl-1-piperazinyl;

4-ethyl-1-piperazinyl;

1-methyl-4-piperidinyl;

1-acetyl-4-piperidinyl;

1-methyl-4-piperidyl;

1-acetyl-4-piperidyl;

4-*tert*-butoxycarbonylmethyl-1-piperazinyl;

4-isopropoxycarbonylmethyl-1-piperazinyl;

4-carboxymethyl-1-piperazinyl;

4-benzyl-1-piperazinyl;

4-cyanomethyl-1-piperazinyl;

4-benzyloxy-ethyl-1-piperazinyl;

4-ethyl-1-homopiperazinyl;

4-(2-hydroxy-ethyl)-1-piperazinyl;

4-carbamoylmethyl-1-piperazinyl;

4-dimethylcarbamoylmethyl-1-piperazinyl; or

4-diethylcarbamoylmethyl-1-piperazinyl.

In a most preferred embodiment, the benzimidazole derivative of the invention is

2-Methoxyethyl 1-(3-(4-(ethoxy-carbonyl)-1-piperazinylmethyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(ethoxy-carbonyl-methyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-carboxymethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Metoxyethyl 1-(3-(4-acetyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(1-methyl-4-piperidyl)phenyl)benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(1-acetyl-4-piperidyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-*t*-butoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-*i*-propoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-[4-(3-(5-Methoxycarbonylbenzimidazol-1-yl)-phenyl)-1-piperazinyl]-acetic acid;

2-(Methylthio)-ethyl 1-(3-(4-methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-(N,N-dimethylamino)-ethyl 1-(3-(1-carboxymethyl-4-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-benzyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

Methyl 1-(3-(4-cyanomethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-cyanomethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

Methyl 1-(3-(4-benzyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-benzyloxyethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-ethyl-1-homopiperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methyl 1-(3-(4-ethyl-1-homopiperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-ethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-(2-hydroxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

Methyl 1-(3-(1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-methoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-ethoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-diethylcarbamoylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-methoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-carbamoylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-carbamoylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-diethylcarbamoylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-carboxymethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

5-(3-Furanyl)-1-(3-((4-ethoxycarbonyl-1-piperazinyl)-methyl)-phenyl)-benzimidazole;

5-(3-Furanyl)-1-(3-(1-(ethoxy-carbonyl-methyl)-4-piperazinyl)-phenyl)-benzimidazole;

5-(3-Furanyl)-1-(3-(4-t-butoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole;

5-(3-Furanyl)-1-(3-(1-ethoxycarbonylmethyl-4-piperazinylmethyl)-phenyl)-benzimidazole;

5-(3-Furanyl)-1-(3-(1-ethoxycarbonylmethyl-4-piperidyl)-phenyl)-benzimidazole;

5-(3-Furanyl)-1-(3-(4-ethoxycarbonylpiperid-1-ylmethyl)-phenyl)-benzimidazole; or

5-(3-Furanyl)-1-(3-(1-ethoxycarbonyl-4-piperazinyl)-phenyl)-benzimidazole;

or a pharmaceutically acceptable salt thereof.

Definition of Substituents

In the context of this invention halogen represents a fluorine, a chlorine, a bromine or an iodine atom.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably consists of from one to eight carbon atoms (C_{1-8}-alkyl), more preferred from one to six carbon atoms (C_{1-6}-alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In a preferred embodiment of this invention alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C_{3-7}-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In the context of this invention an alkenyl group designates a carbon chain containing one or more double bonds, including di-enes, tri-enes and poly-enes. In a preferred embodiment the alkenyl group of the invention comprises of from two to six carbon atoms (C_{2-6}-alkenyl), including at least one double bond. In a most preferred embodiment the alkenyl group of the invention is ethenyl; 1,2- or 2,3-propenyl; or 1,2-, 2,3-, or 3,4-butenyl.

In the context of this invention an alkynyl group designates a carbon chain containing one or more triple bonds, including di-ynes, tri-ynes and poly-ynes. In a preferred embodiment the alkynyl group of the invention comprises of from two to six carbon atoms (C_{2-6}-alkynyl), including at least one triple bond. In its most preferred embodiment the alkynyl group of the invention is ethynyl, 1,2- or 2,3-propynyl, 1,2-, 2,3- or 3,4-butynyl.

In the context of this invention an alkoxy-alkyl group designates an "alkyl-O-alkyl-" group, wherein alkyl is as defined above.

In the context of this invention a thioalkoxy-alkyl group designates an "alkyl-S-alkyl" group wherein alkyl is as defined above;

In the context of this invention an alkoxyalkoxy group designates O-alkyl-O-alkyl wherein alkyl is as defined above.

In the context of this invention an thioalkoxy-alkoxy group designates O-alkyl-S-alkyl wherein alkyl is as defined above.

In the context of this invention an acyl group designates a carboxy group (HOOC-), an alkyl-carbonyl group (alkyl-CO-), or a cycloalkyl-carbonyl (cycloalkyl-CO-), wherein alkyl and cycloalkyl are as defined above. Examples of preferred acyl groups of the invention include carboxy, acetyl, and propionyl.

In the context of this invention an aryl group designates a monocyclic or polycyclic aromatic hydrocarbon group. Examples of preferred aryl groups of the invention include phenyl, naphthyl and anthracenyl.

In the context of this invention an aralkyl group designates a mono- or polycyclic aryl group as defined above, which aryl group is attached to an alkyl group as also defined above. Examples of preferred aralkyl groups of the invention include benzyl, and phenethyl.

In the context of this invention a "Heterocycle" designates a mono- or polycyclic heterocyclic group, which is a mono- or polycyclic group, and which group holds one or more heteroatoms in its ring structure. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S). One or more of the ring structures may in particular be aromatic (i.e. a heteroaryl), saturated or partially saturated. Preferred heterocyclic monocyclic groups of the invention include 5- and 6-membered heterocyclic monocyclic groups. Preferred poly-heterocyclic groups of the invention are the bicyclic heterocyclic groups.

Examples of preferred aromatic heterocyclic 5-membered monocyclic groups of the invention include

furan, in particular 2- or 3-furanyl;
thiophene, in particular 2- or 3-thienyl;
pyrrole (azole), in particular 1-, 2- or 3-pyrrolyl;
oxazole, in particular oxazol-(2-,4- or 5-)yl;
thiazole, in particular thiazol-(2-,4-, or 5-)yl;
imidazole, in particular imidazol-(1-,2-,4- or 5-)yl;
pyrazole, in particular pyrazol-(1-,3-,4- or 5-)yl;
isoxazole, in particular isoxazol-(3-,4- or 5-)yl;
isothiazole, in particular isothiazol-(3-,4- or 5-)yl;
1,2,3-oxadiazole, in particular 1,2,3-oxadiazol-(4- or 5-)yl;
1,2,4-oxadiazole, in particular 1,2,4-oxadiazol-(3- or 5-)yl;
1,2,5-oxadiazole, in particular 1,2,5-oxadiazol-(3- or 4-)yl;
1,2,3-triazole, in particular 1,2,3-triazol-(1-,4- or 5-)yl;
1,2,4-thiadiazole, in particular 1,2,4-thiadiazol-(3- or 5-)yl;
1,2,5-thiadiazole, in particular 1,2,5-thiadiazol-(3- or 4-)yl; and
1,3,4-thiadiazole, in particular 1,3,4-thiadiazol-(2- or 5-)yl.

Examples of preferred saturated or partially saturated heterocyclic monocyclic 5-membered groups of the invention include

1,3-dioxolan, in particular 1,3-dioxolan-(2- or 4-)yl;
imidazolidine, in particular imidazolidin-(1-,2-,3-,4- or 5-)yl;
2-imidazoline, in particular 2-imidazolin-(1-,2-,4- or 5-)yl;
3-imidazoline, in particular 3-imidazolin-(1-,2-,4- or 5-)yl;
4-imidazoline, in particular 4-imidazolin-(1-,2-,4- or 5-)yl;
2H-oxazole (oxazoline), in particular 2H-oxazol-(2-,4- or 5-)yl;
4H-oxazole (oxazolidine), in particular 4H-oxazol-(2-,4- or 5-)yl;

1,2,3-oxadiazoline, in particular 1,2,3-oxadiazol-(4- or 5-)yl;
1,2,4-oxadiazoline, in particular 1,2,4-oxadiazol-(3- or 5-)yl;
1,2,5-oxadiazoline, in particular 1,2,5-oxadiazol-(3- or 4-)yl;
1,2,3-oxadiazolidine, in particular 1,2,3-oxadiazol-(4- or 5-)yl;
1,2,4-oxadiazolidine, in particular 1,2,4-oxadiazol-(3- or 5-)yl;
1,2,5-oxadiazolidine, in particular 1,2,5-oxadiazol-(3- or 4-)yl;
2H-pyrrole (pyrroline), in particular 2H-pyrrol-(1-,2- or 3-)yl;
4H-pyrrole (pyrrolidine), in particular 4H-pyrrol-(1-,2- or 3-)yl;
pyrazolidine, in particular pyrazolidin-(1-,2-,3-,4- or 5-)yl;
2-pyrazoline, in particular 2-pyrazolin-(1-,3-,4- or 5-)yl; and
3-pyrazoline, in particular 3-pyrazolin-(1-,3-,4- or 5-)yl.

Examples of preferred aromatic heterocyclic 6-membered monocyclic groups of the invention include

pyridine, in particular pyridin-(2-,3- or 4-)yl;
pyridazine, in particular pyridazin-(3- or 4-)yl;
pyrimidine, in particular pyrimidin-(2-,4- or 5-)yl;
pyrazine, in particular pyrazin-(2-,3-,5- or 6-)yl;
1,3,5-triazine, in particular 1,3,5-triazin-(2-,4- or 6-)yl; and
phosphinine, in particular phosphinin-(2-,3- or 4-)yl.

Examples of preferred saturated or partially saturated heterocyclic monocyclic 6-membered groups of the invention include

1,4-dioxolane, in particular 1,4-dioxolan-(2- or 3-)yl;
1,4-dithiane, in particular 1,4-dithian-(2- or 3-)yl;
morpholine, in particular morpholin-(2-,3- or 4-)yl;
1,4-oxazine, in particular 1,4-oxazin-(2-)yl;
oxadiazine, in particular oxadiazin-(2-,3- or 5-)yl;
piperidine, in particular piperidin-(1-,2-,3- or 4-)yl;
piperazine, in particular piperazin-(1-,2-,3- or 4-)yl;
2H-pyrane, in particular 2H-pyran-(2-,3- or 4-)yl;
4H-pyrane, in particular 4H-pyran-(2-,3- or 4-)yl;
thiomorpholine, in particular thiomorpholin-(2-,3- or 4-)yl; and
1,3,5-trithiane, in particular 1,3,5-trithian-(2-)yl.

Examples of preferred saturated or partially saturated heterocyclic monocyclic 7-membered groups of the invention include

homopiperidine, in particular homopiperidin-(1-,2-,3- or 4-)yl; and
homopiperazine, in particular homopiperazin-(1-,2-,3- or 4-)yl.

Examples of preferred aromatic heterocyclic bi-cyclic groups of the invention include

indolizine, in particular indolizin-(1-,2-,3-,5-,6-,7- or 8)yl;

indole, in particular indol-(1-,2-,3-,4-,5-,6- or 7)yl;
isoindole, in particular isoindol-(1-,2-,3-,4-,5-,6- or 7-)yl;
benzo[b]furan (benzofuran), in particular benzo[b]furan-(2-,3-,4-,5-,6- or 7-)yl;
benzo[c]furan (isobenzofuran), in particular benzo[c]furan-(1-,3-,4-,5-,6- or 7-)yl;
benzo[b]thiophene (benzothiophene), in particular benzo[b]thiophen-(2-, 3-,4-,5-,6- or 7-)yl;
benzo[c]thiophene (isobenzothiophene), in particular benzo[c]thiophen-(1-,3-,4-,5-,6- or 7-)yl;
benzimidazole, in particular benzimidazol-(1-,2-,4-,5-,6- or 7-)yl;
benzthiazole, in particular benzthiazol-(2-,4-,5-,6- or 7-)yl;
purine, in particular purin-(2-,6- or 8-)yl;
quinoline, in particular quinolin-(2-,3-,4-,5-,6-,7- or 8-)yl;
isoquinoline, in particular isoquinolin-(1-,3-,4-,5-,6-,7- or 8-)yl;
cinnoline, in particular cinnolin-(3-,4-,5-,6-,7- or 8-)yl;
phthlazine, in particular phthlazin-(1-,4-,5-,6-,7- or 8-)yl;
quinazoline, in particular quinazolin-(2-,4-,5-,6-,7- or 8-)yl;
quinoxaline, in particular quinoxalin-(2-,3-,5-,6-,7- or 8-)yl;
1,8-naphthyridine, in particular 1,8-naphthyridin-(2-,3-,4-,5-,6- or 7-)yl; and
pteridine, in particular pteridin-(2-,4-,6- or 7-)yl.

Examples of preferred aromatic heterocyclic tri-cyclic groups of the invention include

carbazole, in particular carbazol-(1-,2-,3-,4-,5-,6-,7-,8- or 9-)yl;
acridine, in particular acridin-(1-,2-,3-,4-,5-,6-,7-,8- or 9-)yl;
phenazine, in particular phenazin-(1-,2-,3-,4-,6-,7-,8- or 9-)yl;
phenothiazine, in particular phenothiazin-(1-,2-,3-,4-,6-,7-,8-,9- or 10-)yl; and
phenoxazine, in particular phenoxazin-(1-,2-,3-,4-,6-,7-,8-,9- or 10-)yl.

Examples of preferred saturated or partially saturated heterocyclic bi-cyclic groups of the invention include

indoline, in particular indolin-(1-,2-,3-,4-,5-,6- or 7-)yl;
3H-indole, in particular 3H-indol-(2-,3-,4-,5-,6- or 7-)yl;
1H-indazole, in particular 1H-indazol-(3-,4-,5-,6- or 7-)yl;
4H-quinolizine, in particular 4H-quinolizin-(1-,2-,3-,4-6-,7-,8- or 9-)yl;
quinuclidine, in particular quinuclidin-(2-,3-,4-,5-,6-,7- or 8-)yl;
isoquinuclidine, in particular isoquinuclidin-(1-,2-,3-,4-,5-,6-,7- or 8-)yl;
tropane, in particular tropan-(1-,2-,3-,4-,5-,6-,7- or 8-)yl; and
nortropane, in particular nortropan-(1-,2-,3-,4-,5-,6- or 7-)yl.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzensulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

Metal salts of a chemical compound of the invention includes alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

In the context of this invention the "onium salts" of N-containing compounds are also contemplated as pharmaceutically acceptable salts. Preferred "onium salts" include the alkyl-onium salts, the cycloalkyl-onium salts, and the cycloalkylalkyl-onium salts.

The chemical compound of the invention may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvents such as

water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

Steric Isomers

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Moreover, some of the chemical compounds of the invention may exist in two forms, cis- and trans-form (Z- and E-form), depending on the arrangement of the substituents around the -C=C- double bond. A chemical compound of the present invention may thus be the cis- or the trans-form (Z- and E-form), or it may be a mixture hereof.

Methods of Preparation

The benzimidazole derivatives of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present

application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the benzimidazole derivative of the invention.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefor, and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semi-permeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

The chemical compound of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the

same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The chemical compound of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing pharmaceutical compositions from a chemical compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The chemical compound according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compound of the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia

or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

A therapeutically effective dose refers to that amount of active ingredient which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED_{50} and LD_{50}, may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD_{50}/ED_{50}. Pharmaceutical compositions which exhibit large therapeutic indexes are preferred.

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

The actual dosage depend on the nature and severity of the disease being treated and the route of administration, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

As the preferred way of administration is intravenous and by infusion the dose ranges are from 0.01µg/kg/h to about 10 mg/kg/h.

Biological Activity

It is an object of the present invention to provide compounds capable of modulating the $GABA_A$ receptor complex, which object is met by the provision of the novel benzimidazole derivatives of Formula I.

The benzimidazole derivatives of the invention are particularly useful as anaesthetics and/or pre-anaesthetics, for inducing and maintaining anaesthesia, as sedatives, as muscle relaxants, and for combating febrile convulsions in children, status epilepticus, for use to patients constrained to a respirator.

The benzimidazole derivatives of the invention show a short duration of action, they are water soluble at therapeutic relevant doses, and are particular well suited for intravenous administration.

The compounds of the invention may also be used by veterinarians.

As demonstrated in the working examples the benzimidazole derivatives of the invention show high to moderate affinity for the benzodiazepine receptor as measured by displacement at ^{3}H-flunitrazepam *in vitro* as well as *in vivo*. The most preferred compounds are full agonists i.e. they exert a high maximal effect in the seizure test as described in the application.

Preferred compounds are full agonists on the $GABA_A$ receptor complex, e.g. as measured by the anticonvulsant activity in the ptz-test described in Example 14, and give rise to a 2-5 fold increase of the tolerated ptz dose. The most preferred compounds are those which increase the tolerated dose the most.

The benzimidazole derivatives of the invention show half-lives of below 30 minutes, which allows for a short duration of action. Preferred half-lives are in the range of from about 30 seconds to about 20 minutes. Most preferred half-lives are in the range of from about 2 to about 5 minutes.

The preferred compounds induce a rapid onset of anaesthesia, i.e. in less than 1-2 minutes. Most preferred is an onset of anaesthesia in less than 1 minute.

Awakening from anaesthesia following a bolus injection (i.v.), or following the attenuation of an infusion, should occur within a short period of time, i.e. of from about 5 to about 30 minutes, preferably of from about 5 to about 10 minutes, after which time the patient should normalise rapidly, i.e. in less than 40 minutes, preferably in less than 20 minutes, as measured from awakening.

The compounds of this invention can be used together with analgetic compounds such as Remifentanile, Fentanyl, or other opiods.

Methods of Therapy

In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to modulation of the GABA receptor complex, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of benzimidazole derivative of the invention.

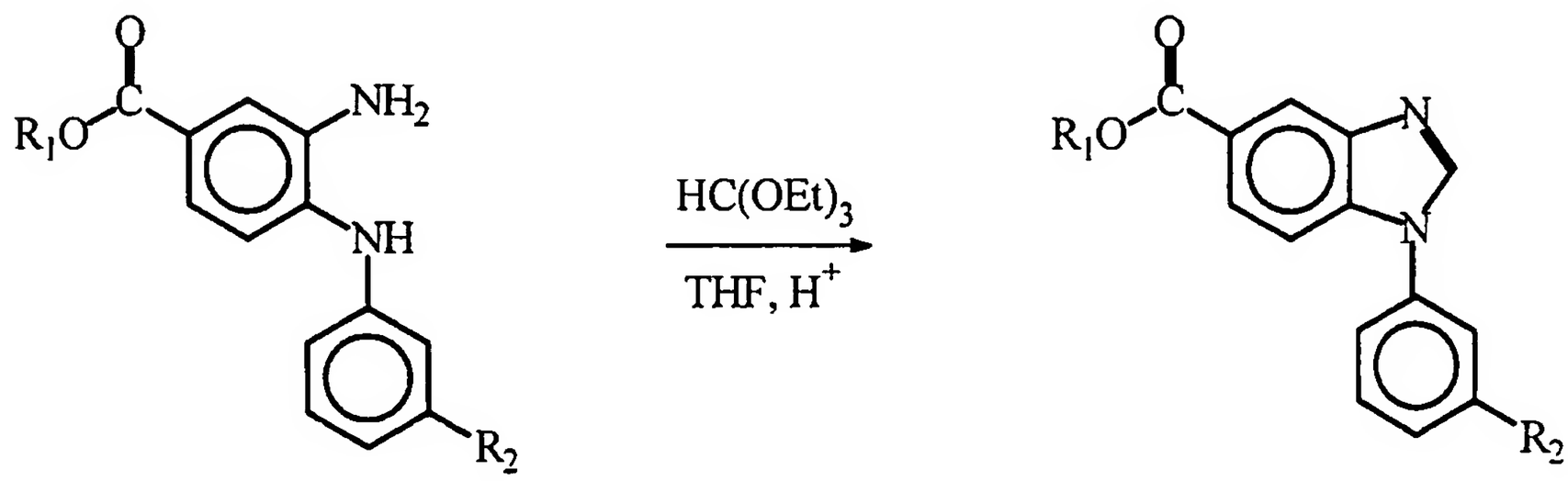
In a more preferred embodiment the invention provides a method for the induction or maintenance of anaesthesia or pre-anaesthesia, muscle relaxation or sedation, or for the treatment, prevention or alleviation of fewer cramps or status epilepticus.

It is at present contemplated that suitable infusion rates are in the range of from about 0.01 to about 100 mg/kg/hour, more preferred of from about 0.1 to about 15 mg/kg/hour, dependent upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

The invention is further illustrated with reference to the following examples which are not intended to be in any way limiting to the scope of the invention as claimed.

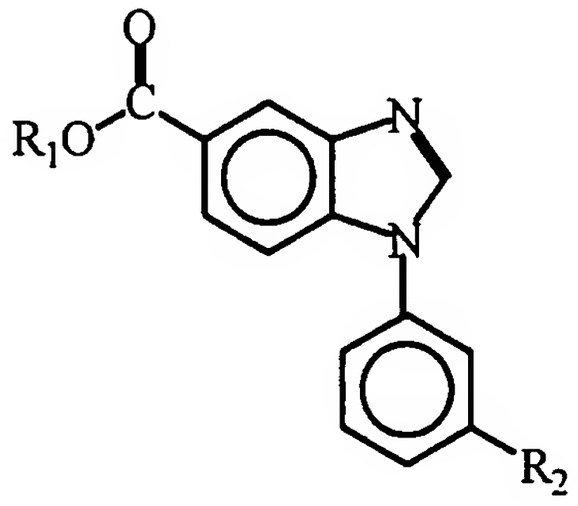
Example 1

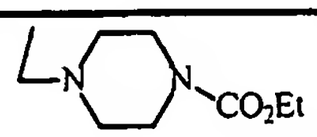
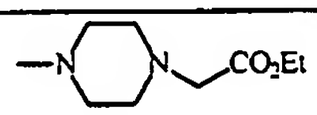
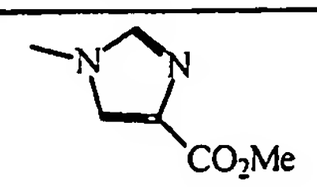
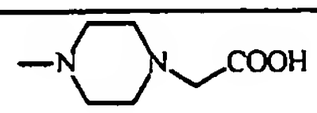
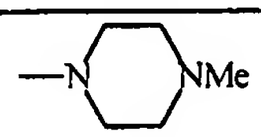
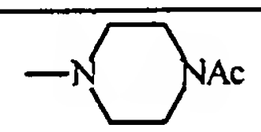
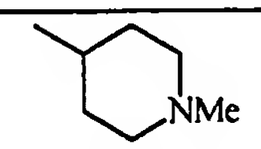
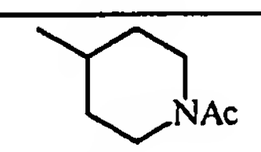
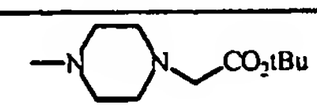
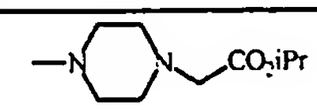
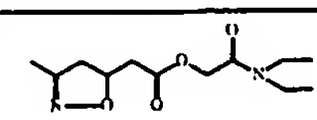
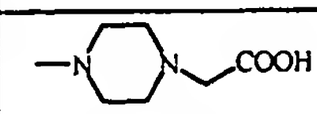
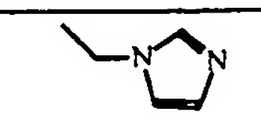
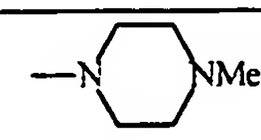
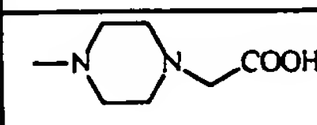
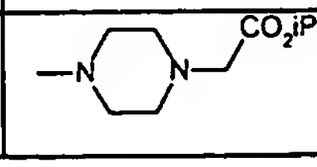


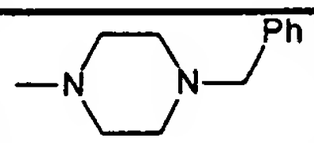
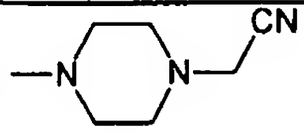
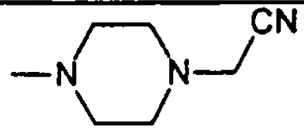
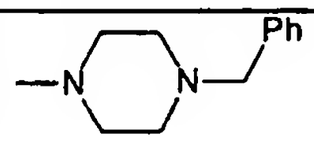
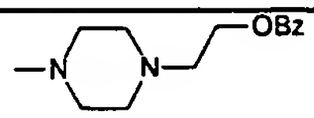
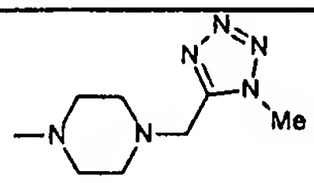
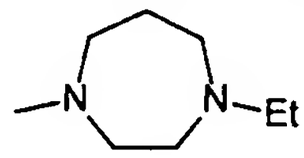
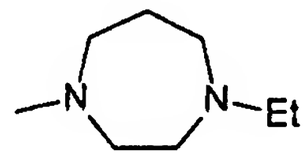
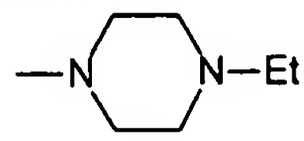
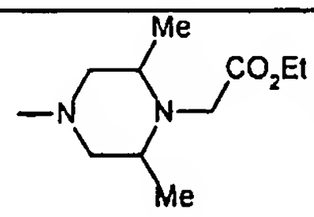
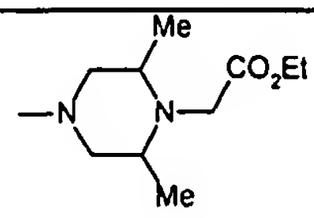
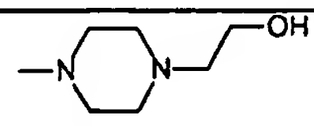
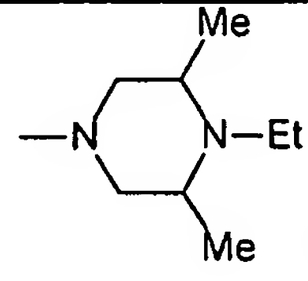
2 **1**

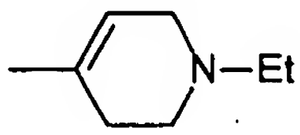
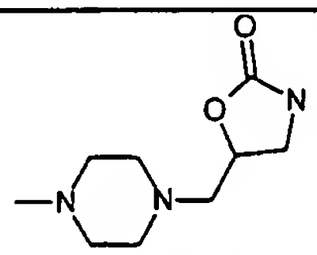
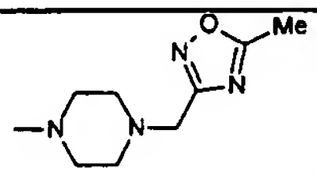
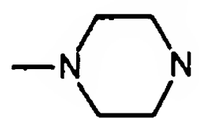
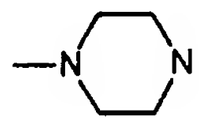
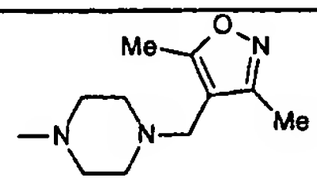
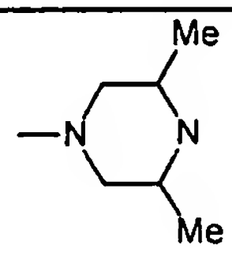
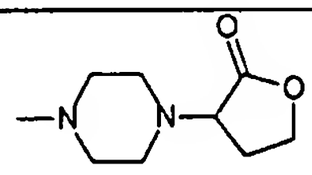
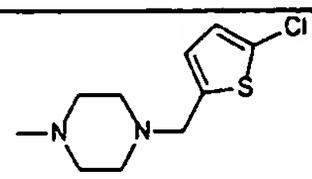
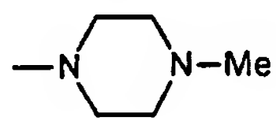
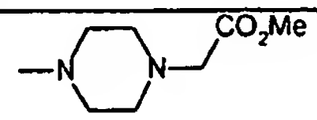
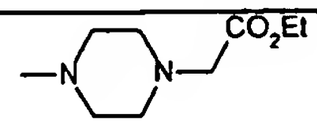
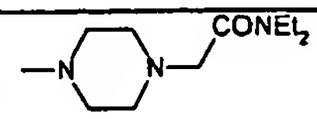
The benzimidazoles of Table 1 were all prepared according to the above scheme as exemplified for compound **1a**, below.

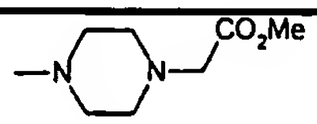
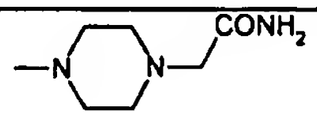
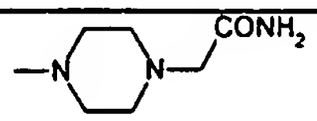
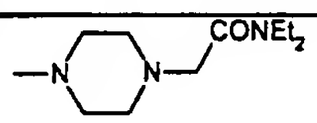
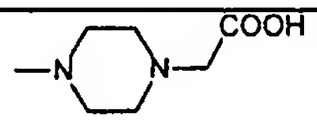
Table 1



Comp. No.	R_1	R_2	Mp (°C)	Yield (%)	Starting material	Salt
1a	$MeO(CH_2)_2$		171-173	48	**2a**	HCl
1b	$MeO(CH_2)_2$		161-163	64	**2b**	HCl
1c	$MeO(CH_2)_2$		132-134	78	**2c**	HCl
1d	$MeO(CH_2)_2$		105-110	43	**2d**	-
1e	$MeO(CH_2)_2$		136-137	29	**2e**	male-ate
1f	$MeO(CH_2)_2$		157-164	53	**2f**	HCl
1g	$MeO(CH_2)_2$		123-125	27[a]	**2g**	HCl
1h	$MeO(CH_2)_2$		139-140	62	**2h**	HCl
1i	$MeO(CH_2)_2$		218-224	100	**2i**	HCl
1j	$MeO(CH_2)_2$		155-159	69	**2j**	HCl
1k	Et		157-159	70	**2k**	HCl
1l	Me		241-244	42	**2l**	HCl
1m	Me		210-220	2	**2m**	HCl
1n	$MeS(CH_2)_2$		71-75	42	**2n**	-
1o	$MeS(CH_2)_2$		121-122	69	**2o**	-
1p	$Me_2N(CH_2)_2$		47 (de-comp.)	30	**2p**	-
1q	$MeO(CH_2)_2$		155-159	69	**2q**	HCl

Comp. No.	R_1	R_2	Mp (°C)	Yield (%)	Starting material	Salt
1r	$MeO(CH_2)_2$		172-177	75	**2r**	HCl
1s	Me		160-162	53	**2s**	-
1t	$MeO(CH_2)_2$		91-93	71	**2t**	-
1u	Me		153-163	70	**2u**	HCl
1v	$MeO(CH_2)_2$		139-141	45	**2v**	HCl
1w	$MeO(CH_2)_2$		196-198	73	**2w**	HCl
1x	$MeO(CH_2)_2$		un-defined	72	**2x**	HCl
1y	Me		un-defined	66	**2y**	HCl
1z	$MeO(CH_2)_2$		166-168	26	**2z**	HCl
1aa	$MeO(CH_2)_2$		90-94	59	**2aa**	HCl
1bb	Me		168-181	48	**2bb**	HCl
1cc	$HO(CH_2)_2$		182-192	34	**2cc**	HCl
1dd	$MeO(CH_2)_2$		202-208	24	**2dd**	HCl

Comp. No.	R_1	R_2	Mp (°C)	Yield (%)	Starting material	Salt
1ee	$MeO(CH_2)_2$		179-180	69	**2ee**	HCl
1ff	$MeO(CH_2)_2$		oil	54	**2ff**	HCl
1gg	$MeO(CH_2)_2$		oil	100	**2gg**	-
1hh	Me		179-202	81	**2hh**	2HCl
1ii	$MeO(CH_2)_2$		191-205	74	**2ii**	2HCl
1jj	$MeO(CH_2)_2$		219-223	50	**2jj**	HCl
1kk	$MeO(CH_2)_2$		215-231	92	**2kk**	HCl
1ll	$MeO(CH_2)_2$		225-254	60	**2ll**	HCl
1mm	$MeO(CH_2)_2$		185-186	62	**2mm**	HCl
1nn	$HO(CH_2)_2$		128-139	17	**2nn**	HCl
1oo	$HO(CH_2)_2$		150-155	44	**2oo**	HCl
1pp	$HO(CH_2)_2$		103-125	45	**2pp**	HCl
1qq	$MeO(CH_2)_2$		202-204	100	**2qq**	HCl

Comp. No.	R_1	R_2	Mp (°C)	Yield (%)	Starting material	Salt
1rr	$MeO(CH_2)_2$		161-164	72	**2rr**	HCl
1ss	$MeO(CH_2)_2$		211-212	58	**2ss**	HCl
1tt	$HO(CH_2)_2$		268-270	79	**2tt**	HCl
1uu	$HO(CH_2)_2$		149-154	64	**2uu**	HCl
1vv	$HO(CH_2)_2$		un-defined	50	**2vv**	HCl

[a]the total yield from three steps.

2-Methoxyethyl 1-(3-(4-(ethoxy-carbonyl)-1-piperazinylmethyl)-phenyl)-benzimidazole-5-carboxylate (**1a**): A mixture of **2a** (0.57 g; 1.25 mmol), triethylorthoformate (0.42 ml; 2.5 mmol) and a catalytic amount of p-toluenesulfonic acid in tetrahydrofurane (10 ml) was heated to reflux for 30 min. The cooled mixture was diluted with ethyl acetate and washed with aqueous sodium hydroxide (1 M). The organic phase was dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column-chromatography on silica gel using ethyl acetate as the eluent. The product was precipitated as the hydrochloride by addition of etheral hydrogen chloride to the eluate. Yield: 0.4 g (64%). Mp. 171-173°C.

The following compound were prepared in analogy with Compound **1a**:

2-Methoxyethyl 1-(3-(4-(ethoxy-carbonyl-methyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1b**) from **2b**. A mixture of ethyl acetate and acetone (4:1 v/v) was used as the eluent. Mp. 161-163°C.

2-Methoxyethyl 1-(3-(4-methoxycarbonyl-1-imidazolyl)-phenyl)-benzimidazole-5-carboxylate (**1c**) from **2c**. Mp. 132-134°C.

2-Methoxyethyl 1-(3-(4-carboxymethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1d**) from **2d**. Mp. 105-110°C. A mixture of acetonitrile, acetic acid and water (8:1:1 v/v/v) was used as the eluent for the column chromatographic purification. No hydrogen chloride was added.

2-Methoxyethyl 1-(3-(4-methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1e**) from **2e**. Mp. 136-137°C isolated as the maleate. A mixture of ethyl acetate and acetone (4:1 v/v) was used as the eluent.

2-Metoxyethyl 1-(3-(4-acetyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1f**) from **2f**. Mp. 157-164°C. A mixture of ethyl acetate and acetone (4:1 v/v) was used as the eluent.

2-Methoxyethyl 1-(3-(1-methyl-4-piperidyl)-phenyl)-benzimidazole-5-carboxylate (**1g**) from **2g**. Mp. 123-125°C. A mixture of ethyl acetate and acetone (4:1 v/v) was used as the eluent.

2-Methoxyethyl 1-(3-(1-acetyl-4-piperidyl)-phenyl)-benzimidazole-5-carboxylate (**1h**) from **2h**. Mp. 139-140°C. Acetone was used as the eluent for the column-chromatographic purification.

2-Methoxyethyl 1-(3-(4-*t*-butoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1i**) from **2i**. Mp. 218-224°C.

2-Methoxyethyl 1-(3-(4-*i*-propoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1j**) from **2j**. Mp. 155-159°C.

((N,N-Diethylcarbamoyl)-methyl 2-(3-[3-(5-ethoxycarbonyl-1-benzimidazolyl)-phenyl]-4,5-dihydroxyisoxazol-5-yl)-acetate (**1k**) from **2k**. Mp. 157-159°C.

Methyl 1-(3-(1-imidazolylmethyl)-phenyl)-benzimidazole-5-carboxylate (**1l**) from **2l**. Mp. 241-244°C. A mixture of dichloromethane and methanol (9:1 v/v) was used as the eluent.

2-[4-(3-(5-Methoxycarbonylbenzimidazol-1-yl)-phenyl)-1-piperazinyl]-acetic acid (**1m**) from **2m**. Mp. 210-220°C. The product was chromatographied twice using a mixture of acetonitrile, water and acetic acid (8:1:1 v/v/v) as the eluent.

2-(Methylthio)-ethyl 1-(3-(1-imidazolylmethyl)-phenyl)-benzimidazole-5-carboxylate (**1n**) from **2n**. Mp. 71-75°C. A mixture of dichloromethane, methanol and aqueous ammonia (90:10:1 v/v/v) was used as the eluent. Isolated as the free base.

2-(Methylthio)-ethyl 1-(3-(4-methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1o**) from **2o**. Mp. 121-122°C.

2-(N,N-dimethylamino)-ethyl 1-(3-(1-carboxymethyl-4-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1p**) from **2p**. Mp. 47°C (with decomposition). A mixture of acetonitrile, acetic acid, pyridine and water (7:1:1:1 v/v/v/v) was used as the eluent.

2-Methoxyethyl 1-(3-(1-isopropoxycarbonylmethyl-4-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1q**) from **2q**. Mp. 155-159°C.

2-Methoxyethyl 1-(3-(4-benzyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1r**) from **2r**. Mp. 172-177°C.

Methyl 1-(3-(4-cyanomethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1s**) from **2s**. Mp. 160-162°C. The product was isolated as the free base.

2-Methoxyethyl 1-(3-(4-cyanomethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1t**) from **2t**. Mp. 91-93°C. The product was isolated as the free base.

Methyl 1-(3-(4-benzyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1u**) from **2u**. Mp. 153-163°C.

2-Methoxyethyl 1-(3-(4-benzyloxyethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1v**) from **2v**. Mp. 139-141°C.

2-Methoxyethyl 1-(3-(4-(1-methyl-5-tetrazolyl)methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1w**) from **2w**. Mp. 196-198°C.

2-Methoxyethyl 1-(3-(4-ethyl-1-homopiperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1x**) from **2x**. Mp. undefined. A mixture of dichloromethane and methanol (9:1 v/v) was used as the eluent.

2-Methyl 1-(3-(4-ethyl-1-homopiperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1y**) from **2y**. Mp. undefined. A mixture of dichloromethane and methanol (9:1 v/v) was used as the eluent.

2-Methoxyethyl 1-(3-(4-ethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1z**) from **2z.** Mp. 166-168°C.

2-Methoxyethyl 1-(3-(4-ethoxycarbonylmethyl-3,5-dimethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1aa**) from **2aa.** Mp. 90-94°C.

2-Methyl 1-(3-(4-ethoxycarbonylmethyl-3,5-dimethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1bb**) from **2bb.** Mp. 168-181°C.

2-Hydroxyethyl 1-(3-(4-(2-hydroxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1cc**) from **2cc**. Mp. 182-192°C. A mixture of ethyl acetate and methanol (1:1 v/v) was used as the eluent.

2-Methoxyethyl 1-(3-(4-ethyl-3,5-dimethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1dd**) from **2dd.** Mp. 202-208°C. A mixture of ethyl acetate and methanol (1:1 v/v) was used as the eluent.

2-Methoxyethyl 1-(3-(1-ethyl-1,2,5,6-tetrahydropyridin-4-yl)-phenyl)-benzimidazole-5-carboxylate (**1ee**) from **2ee**. Mp. 179-180°C.

2-Methoxyethyl 1-(3-(4-(2-oxazolidinone-5-yl)methyl)1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1ff**) from **2ff**. Isolated as an oil.

2-Methoxyethyl 1-(3-(4-(5-methyloxadiazol-3-yl)methyl)1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1gg**) from **2gg**. Isolated as an oil.

Methyl 1-(3-(1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1hh**) from **2hh**. Mp. 179-202°C. The Boc-group was removed subsequently to the ring closure by treatment with trifluoroacetic acid in dichloromethane.

2-Methoxyethyl 1-(3-(1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1ii**) from **2ii**. Mp. 191-205°C. The Boc-group was removed subsequently to the ring closure by treatment with trifluoroacetic acid in dichloromethane.

2-Methoxyethyl 1-(3-(4-(3,5-dimethylisoxazol-4-yl)methyl)1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1jj**) was prepared from **1ii** by alkylation with.4-chloromethyl-3,5-dimethylisoxazol. Mp. 219-223°C.

2-Methoxyethyl 1-(3-(3,5-dimethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1kk**) from **2kk**. Mp. 215-231°C. The Boc-group was removed subsequently to the ring closure by treatment with trifluoroacetic acid in dichloromethane.

2-Methoxyethyl 1-(3-(4-(2-oxo-tetrahydrofuran-3-yl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1ll**) from **2ll**. Mp. 225-254°C.

2-Methoxyethyl 1-(3-(4-(2-chloro-5-thienyl)methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1mm**) was prepared from **1ii** by alkylation with 2-chloromethyl-5-chlorothiophene. Mp. 185-186°C.

2-Hydroxyethyl 1-(3-(4-methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1nn**) from **2nn**. Mp. A mixture of ethyl acetate and methanol (1:1v/v) was used as the eluent.

2-Hydroxyethyl 1-(3-(4-methoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1oo**) from **2oo**. Mp. A mixture of ethyl acetate and methanol (9:1v/v) was used as the eluent.

2-Hydroxyethyl 1-(3-(4-ethoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1pp**) from **2pp**. Mp. A mixture of ethyl acetate and methanol (9:1v/v) was used as the eluent.

2-Methoxyethyl 1-(3-(4-diethylcarbamoylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1qq**) from **2qq**. Mp. 202-204°C. A mixture of ethyl acetate and methanol (9:1v/v) was used as the eluent.

2-Methoxyethyl 1-(3-(4-methoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1rr**) from **2rr**. Mp. 161-164°C. A mixture of ethyl acetate and methanol (9:1v/v) was used as the eluent.

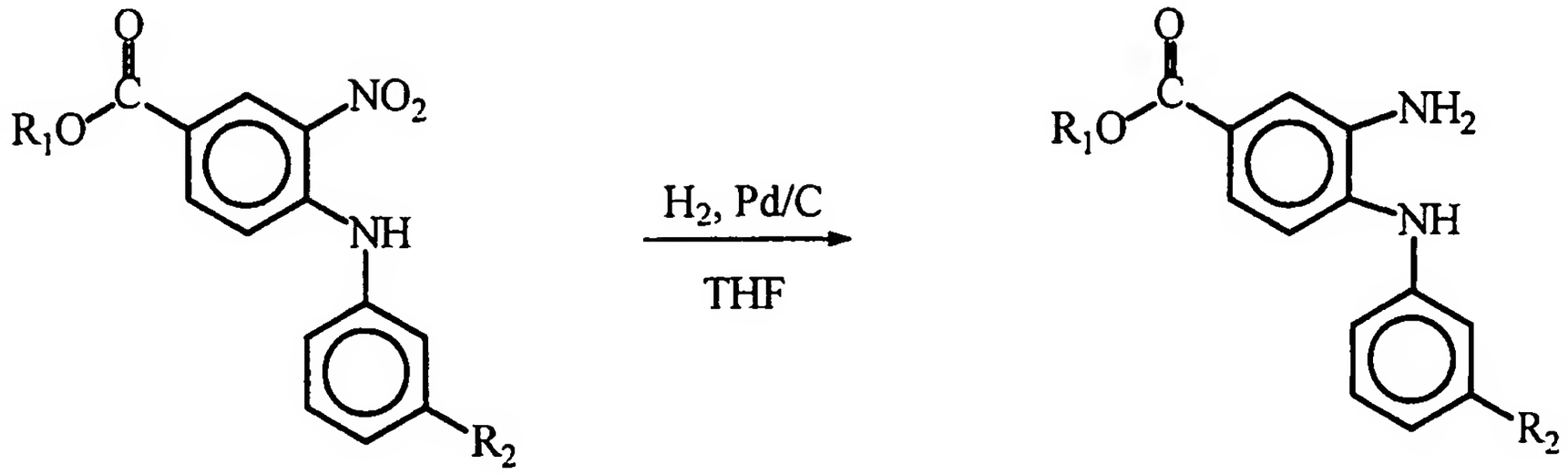
2-Methoxyethyl 1-(3-(4-carbamoylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1ss**) from **2ss**. Mp. 211-212°C. A mixture of ethyl acetate and methanol (9:1v/v) was used as the eluent.

2-Hydroxyethyl 1-(3-(4-carbamoylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1tt**) from **2tt**. Mp. 268-270°C. A mixture of ethyl acetate and methanol (9:1v/v) was used as the eluent.

2-Hydroxyethyl 1-(3-(4-diethylcarbamoylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1uu**) from **2uu**. Mp. 149-154°C. A mixture of ethyl acetate and methanol (9:1v/v) was used as the eluent.

2-Hydroxyethyl 1-(3-(4-carboxymethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1vv**) from **2vv**. DMF was used as the solvent and a mixture of acetonitril, water and acetic acid (8:1:1 v/v/v) was used as the eluent.

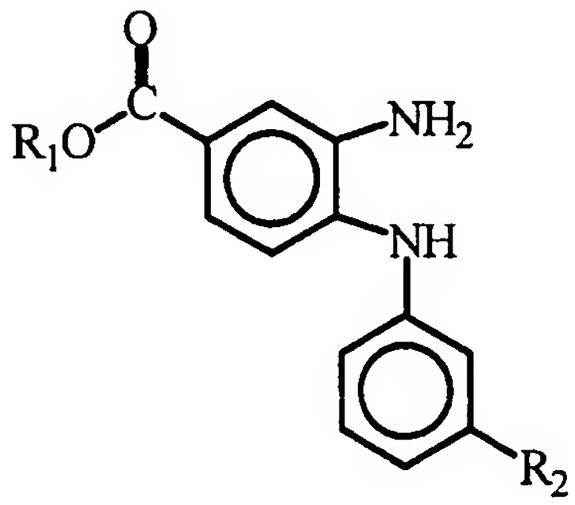
Example 2

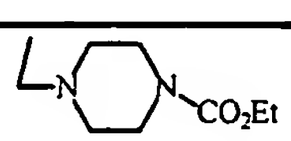
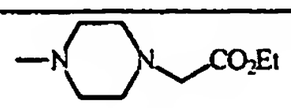
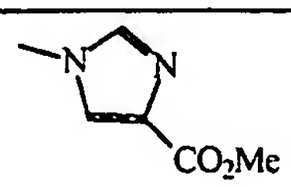
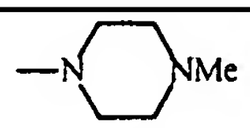
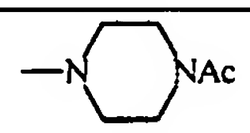


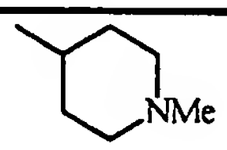
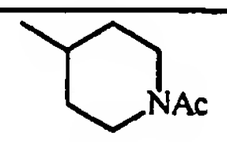
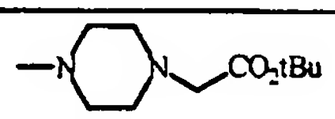
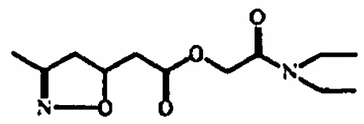
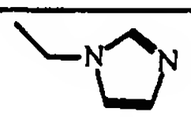
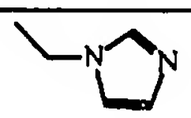
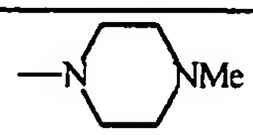
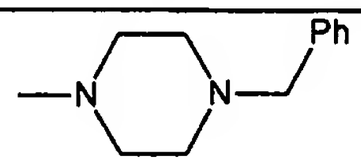
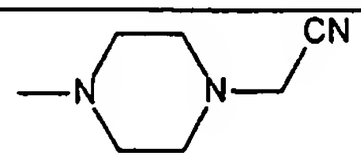
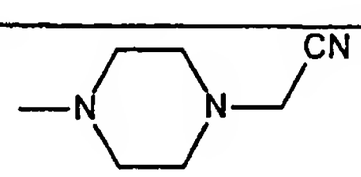
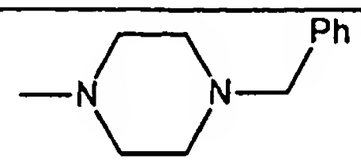
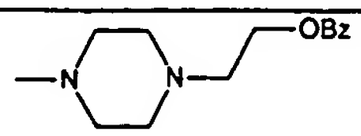
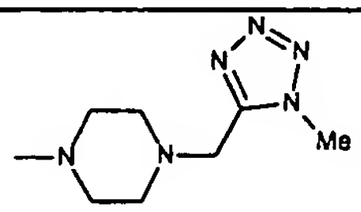
3 2

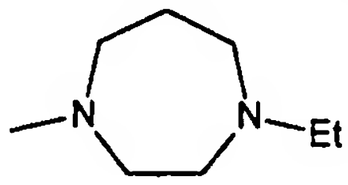
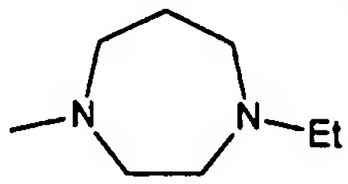
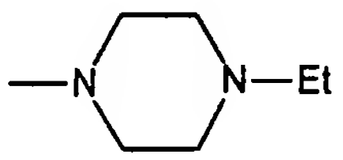
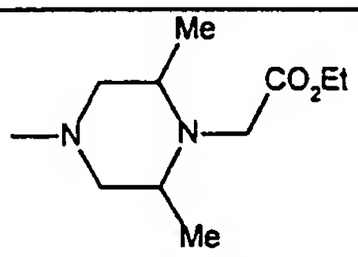
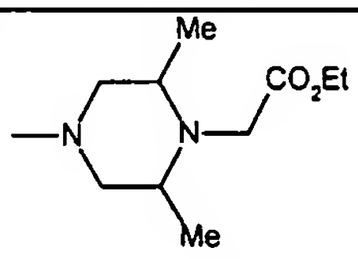
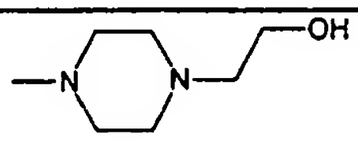
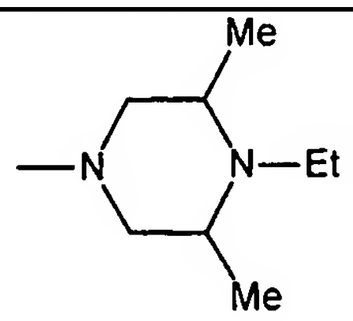
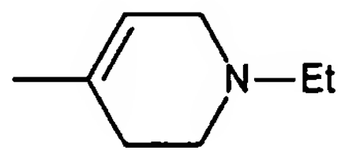
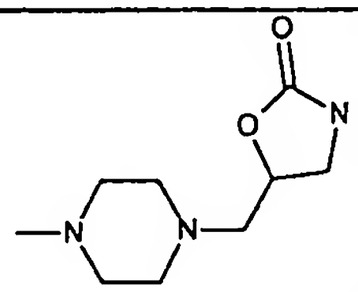
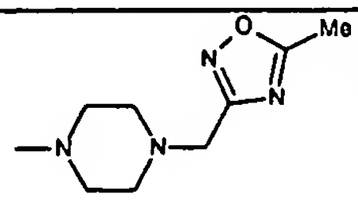
The diamines of Table 2 were all prepared quantitatively by hydrogenation of the corresponding nitroanilines (**3**), according to the above scheme as exemplified for **2a** below.

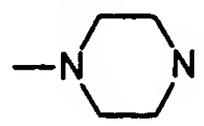
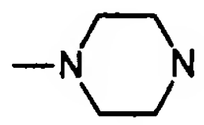
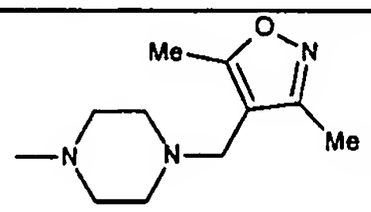
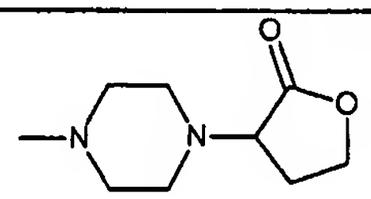
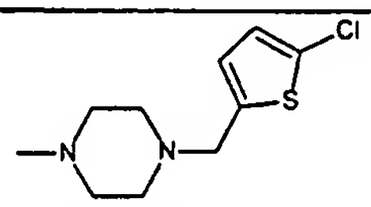
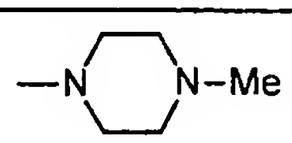
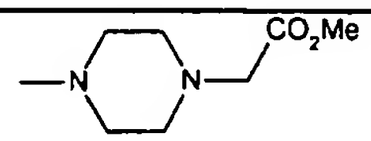
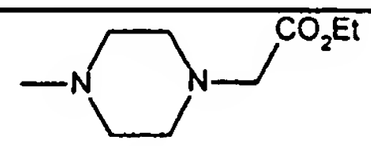
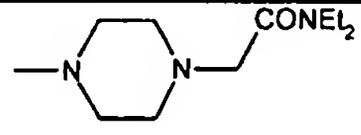
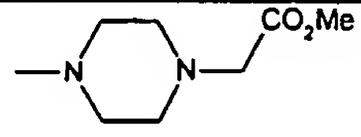
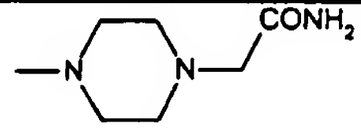
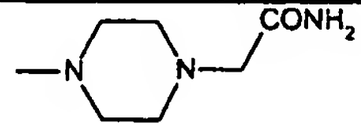
Table 2

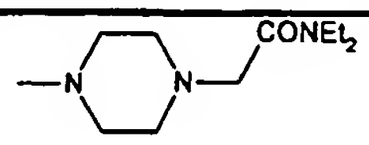
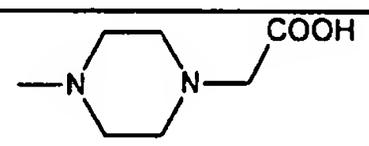


Compound No.	R_1	R_2	Starting material
2a	$MeO(CH_2)_2$		**3a**
2b	$MeO(CH_2)_2$		**3b**
2c	$MeO(CH_2)_2$		**3c**
2e	$MeO(CH_2)_2$		**3e**
2f	$MeO(CH_2)_2$		**3f**

Compound No.	R_1	R_2	Starting material
2g	$MeO(CH_2)_2$		3g
2h	$MeO(CH_2)_2$		3h
2i	$MeO(CH_2)_2$		3i
2j	$MeO(CH_2)_2$		3j
2k	Et		3k
2l	Me		3l
2n	$MeS(CH_2)_2$		3n
2o	$MeS(CH_2)_2$		3o
2r	$MeO(CH_2)_2$		3r
2s	Me		3s
2t	$MeO(CH_2)_2$		3t
2u	Me		3u
2v	$MeO(CH_2)_2$		3v
2w	$MeO(CH_2)_2$		3w

Compound No.	R_1	R_2	Starting material
2x	$MeO(CH_2)_2$		3x
2y	Me		3y
2z	$MeO(CH_2)_2$		3z
2aa	$MeO(CH_2)_2$		3aa
2bb	Me		3bb
2cc	$HO(CH_2)_2$		3cc
2dd	$MeO(CH_2)_2$		3dd
2ee	$MeO(CH_2)_2$		3ee
2ff	$MeO(CH_2)_2$		3ff
2gg	$MeO(CH_2)_2$		3gg

Compound No.	R_1	R_2	Starting material
2hh	Me		3hh
2ii	$MeO(CH_2)_2$		3ii
2jj	$MeO(CH_2)_2$		3jj
2kk	$MeO(CH_2)_2$		3kk
2ll	$MeO(CH_2)_2$		3ll
2mm	$MeO(CH_2)_2$		3mm
2nn	$HO(CH_2)_2$		3nn
2oo	$HO(CH_2)_2$		3oo
2pp	$HO(CH_2)_2$		3pp
2qq	$MeO(CH_2)_2$		3qq
2rr	$MeO(CH_2)_2$		3rr
2ss	$MeO(CH_2)_2$		3ss
2tt	$HO(CH_2)_2$		3tt

Compound No.	R_1	R_2	Starting material
2uu	$HO(CH_2)_2$		**3uu**
2vv	$HO(CH_2)_2$		**3vv**

2-Methoxyethyl 3-amino-4-(3-((1-ethoxycarbonyl-4-piperazinyl)-methyl)-phenylamino)-benzoate (**2a**). **3a** (0.75 g; 1.54 mmol) was suspended in tetrahydrofurane. Palladium catalyst (50 mg, 5% on activated carbon) was added and the mixture was hydrogenated at ambient pressure until the hydrogen uptake had ceased. The mixture was filtered through celite and the filtrate was evaporated to dryness to leave **2a**, quantitatively.

The following compound were prepared in analogy with Compound **2a**:

2-Methoxyethyl 3-amino-4-(3-(1-(ethoxy-carbonyl-methyl)-4-piperazinylmethyl)-phenylamino)-benzoate (**2b**) from **3b**.

2-Methoxyethyl 3-amino-4-(3-(4-methoxycarbonyl-1-imidazolyl)-phenylamino)-benzoate (**2c**) from **3c**.

2-Methoxyethyl 3-amino-4-(3-(1-methyl-4-piperazinyl)-phenylamino)-benzoate (**2e**) from **3e**.

2-Methoxyethyl 3-amino-4-(3-(1-acetyl-4-piperazinyl)-phenylamino)-benzoate (**2f**) from **3f**.

2-Methoxyethyl 3-amino-4-(3-(1-methyl-4-piperidyl)-phenylamino)-benzoate (**2g**) from **3g**.

2-Methoxyethyl 3-amino-4-(3-(1-acetyl-4-piperidyl)-phenylamino)-benzoate (**2h**) from **3h**.

2-Methoxyethyl 3-amino-4-(3-(1-*t*-butoxycarbonylmethyl-4-piperazinyl)-phenylamino)-benzoate (**2i**) from **3i**.

2-Methoxyethyl 3-amino-4-(3-(1-*i*-propoxycarbonylmethyl-4-piperazinyl)-phenylamino)-benzoate (**2j**) from **3j**.

(N,N-Diethylcarbamoyl)-methyl 2-[3-(3-((2-amino-4-ethoxycarbonylphenyl)-amino)-phenyl)-4,5-dihydroisoxazol-5-yl)-acetate (**2k**) from **3k**.

Methyl 3-amino-4-(3-((1-imidazolyl)-methyl)-phenylamino)-benzoate (**2l**) from **3l**.

2-(Methylthio)-ethyl 3-amino-4-(3-(1-imidazolylmethyl)-phenylamino)-benzoate (**2n**) from **3n** using raney nickel as the catalyst.

2-(Methylthio)-ethyl 3-amino-4-(3-(4-methyl-1-piperazinyl)-phenylamino)-benzoate (**2o**) from **3o**.

2-Methoxyethyl 3-amino-4-(3-(1-benzyl-4-piperazinyl)-phenylamino)-benzoate (**2r**) from **3r**. PtO_2 was used as the catalyst.

Methyl 3-amino-4-(3-(1-cyanomethyl-4-piperazinyl)-phenylamino)-benzoate (**2s**) from **3s.**

2-Methoxyethyl 3-amino-4-(3-(1-cyanomethyl-4-piperazinyl)-phenylamino)-benzoate (**2t**) from **3t.** PtO_2 was used as the catalyst.

Methyl 3-amino-4-(3-(1-benzyl-4-piperazinyl)-phenylamino)-benzoate (**2u**) from **3u**. PtO_2 was used as the catalyst.

2-Methoxyethyl 3-amino-4-(3-(1-(2-benzyloxyethyl)-4-piperazinyl)-phenylamino)-benzoate (**2v**) from **3v.** PtO_2 was used as the catalyst.

2-Methoxyethyl 3-amino-4-(3-(1-((1-methyl-5-tetrazolyl)-methyl)-4-piperazinyl)-phenylamino)-benzoate (**2w**) from **3w.** PtO_2 was used as the catalyst.

2-Methoxyethyl 3-amino-4-(3-(1-ethyl-4-homopiperazinyl)-phenylamino)-benzoate (**2x**) from **3x**.

Methyl 3-amino-4-(3-(1-ethyl-4-homopiperazinyl)-phenylamino)-benzoate (**2y**) from **3y.**

2-Methoxyethyl 3-amino-4-(3-(1-ethyl-4-piperazinyl)-phenylamino)-benzoate (**2z**) from **3z**.

2-Methoxyethyl 3-amino-4-(3-((1-(ethoxy-carbonyl-methyl)-2,6-dimethyl)-4-piperazinylmethyl)-phenylamino)-benzoate (**2aa**) from **3aa**.

Methyl 3-amino-4-(3-((1-(ethoxy-carbonyl-methyl)-2,6-dimethyl)-4-piperazinylmethyl)-phenylamino)-benzoate (**2bb**) from **3bb**.

2-Hydroxyethyl 3-amino-4-(3-(1-(2-hydroxyethyl)-4-piperazinyl)-phenylamino)-benzoate (**2cc**) from **3cc**.

2-Methoxyethyl 3-amino-4-(3-((1-ethyl-2,6-dimethyl)-4-piperazinylmethyl)-phenylamino)-benzoate (**2dd**) from **3dd**.

2-Methoxyethyl 3-amino-4-(3-(1-(2-oxazolinon-5-yl)methyl-4-piperazinyl)-phenylamino)-benzoate (**2ff**) from **3ff**.

2-Methoxyethyl 3-amino-4-(3-(1-(5-methyloxadiazol-3-yl)methyl-4-piperazinyl)-phenylamino)-benzoate (**2gg**) from **3gg**. PtO_2 was used as the catalyst.

Methyl 3-amino-4-(3-(1-*boc*-4-piperazinyl)-phenylamino)-benzoate (**2hh**) from **3hh.**

2-Methoxyethyl 3-amino-4-(3-(1-*boc*-4-piperazinyl)-phenylamino)-benzoate (**2ii**) from **3ii.**

2-Methoxyethyl 3-amino-4-(3-(1-*boc*-2,6-dimethyl-4-piperazinyl)-phenylamino)-benzoate (**2kk**) from **3kk.**

2-Methoxyethyl 3-amino-4-(3-(1-(2-oxotetrahydrofuran-3-yl)-4-piperazinyl)-phenylamino)-benzoate (**2ll**) from **3ll.**

2-Hydroxyethyl 3-amino-4-(3-(4-methyl-1-piperazinyl)-phenylamino)-benzoate (**2nn**) from **3nn.**

2-Hydroxyethyl 3-amino-4-(3-(4-methoxycarbonylmethyl-1-piperazinyl)-phenylamino)-benzoate (**2oo**) from **3oo**.

2-Hydroxyethyl 3-amino-4-(3-(4-ethoxycarbonylmethyl-1-piperazinyl)-phenylamino)-benzoate (**2pp**) from **3pp**.

2-Methoxyethyl 3-amino-4-(3-(4-(N,N-diethyl-carbamoyl)methyl-1-piperazinyl)-phenylamino)-benzoate (**2qq**) from **3qq**.

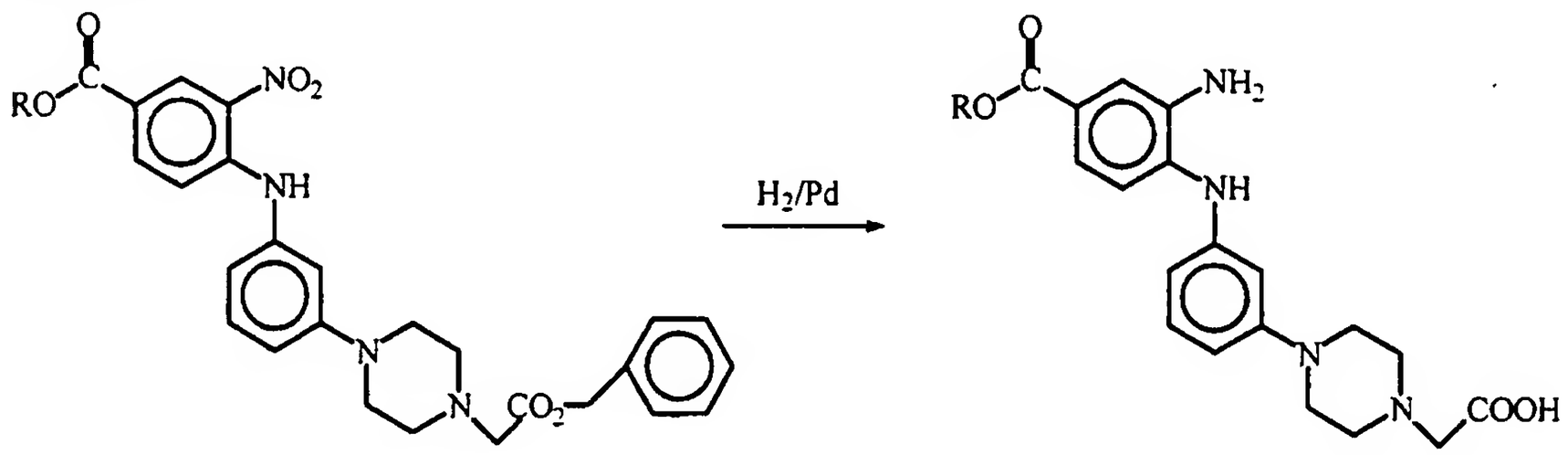
2-Methoxyethyl 3-amino-4-(3-(4-methoxycarbonylmethyl-1-piperazinyl)-phenylamino)-benzoate (**2rr**) from **3rr**.

2-Methoxyethyl 3-amino-4-(3-(4-carbamoylmethyl-1-piperazinyl)-phenylamino)-benzoate (**2ss**) from **3ss**.

2-Hydroxyethyl 3-amino-4-(3-(4-carbamoylmethyl-1-piperazinyl)-phenylamino)-benzoate (**2tt**) from **3tt**.

2-Hydroxyethyl 3-amino-4-(3-(4-(N,N-diethyl-carbamoyl)-methyl-1-piperazinyl)-phenylamino)-benzoate (**2uu**) from **3uu**.

Example 2a.



3d, m, p **2d, m, p**

2-Methoxyethyl 3-amino-4-(3-(1-carboxymethyl-4-piperazinyl)-phenylamino)-benzoate (**2d**). To a solution of 2-methoxyethyl 3-nitro-4-(3-(4-(benzyloxy-carbonyl-methyl)-1-piperazinyl)-phenylamino)-benzoate (**3d**) (3.5 g; 6.4 mmol) in a mixture of tetrahydrofurane (50 ml) and DMF (5 ml) was added palladium catalyst (0.9 g, 5% Pd on activated carbon) and ammonium formiate (0.8 g; 12.6 mmol) and the mixture was heated to reflux for 2 hours. The cooled mixture was filtered through celite and the solvent was removed under reduced pressure to leave **2d**, quantitatively.

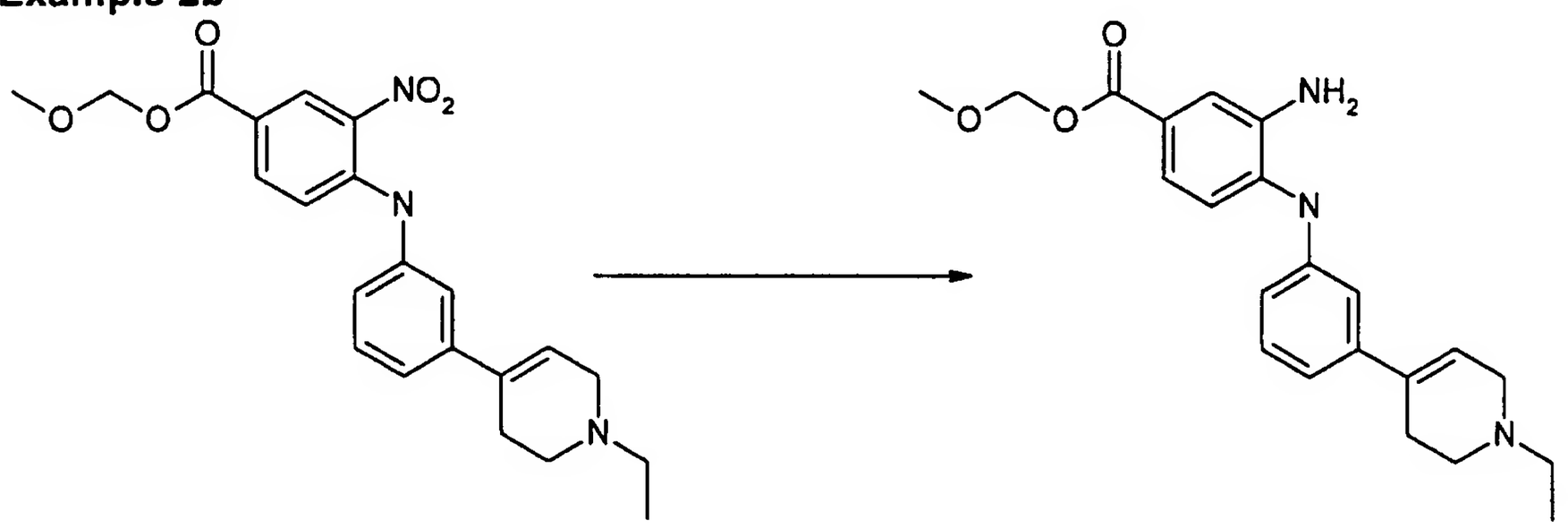
The following compound were prepared in analogy with Compound **2d**:

Methyl 3-amino-4-(3-(1-carboxymethyl-4-piperazinyl)-phenylamino)-benzoate (**2m**) from **3m**.

2-(Dimethylamino)-ethyl 3-amino-4-(3-(1-carboxymethyl-4-piperazinyl)-phenylamino)-benzoate (**2p**) from **3p**.

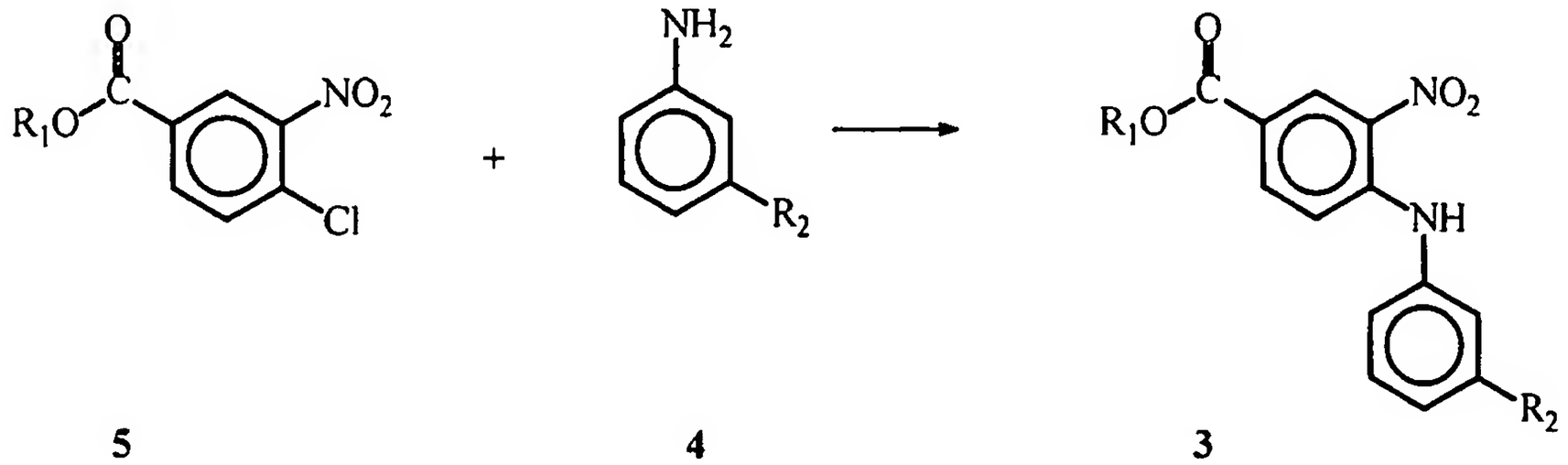
2-Hydroxyethyl 3-amino-4-(3-(1-carboxymethyl-4-piperazinyl)-phenylamino)-benzoate (**2vv**) from **3vv**.

Example 2b



2-Methoxyethyl 3-amino-4-(3-(1-ethyl-1,2,5,6-tetrahydropyridin-4-yl)-phenylamino)-benzoate (**2ee**) from **3ee**. A mixture of **3ee** (0.97 g; 1.9 mmol), sodium sulphide nonahydrate (1.37 g; 5,71 mmol) and ammonium chloride (0.3 g; 5.61 mmol) in a mixture of THF (5 ml) and 2-methoxyethanol (5 ml) was heated to 80°C for two hours. The cooled mixture was poured into ice-water and extracted with ethyl acetate. The extract was dried over magnesium sulphate, filtered and evaporated to dryness. The residue was purified on a silica gel column using a mixture of ethyl acetate and methanol (9:1 v/v) as the eluent. Yield: 0.21 g.

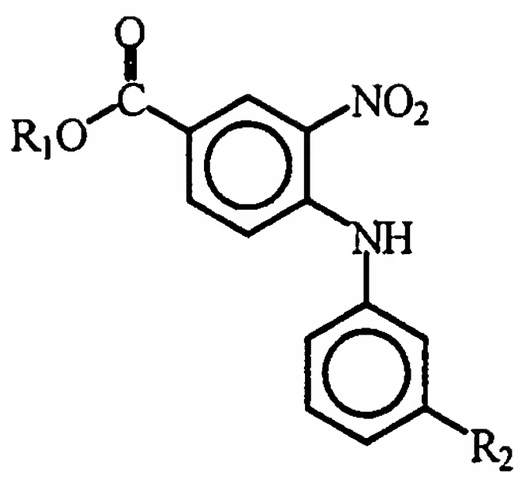
Example 3

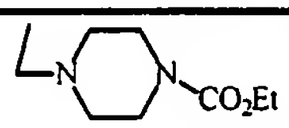
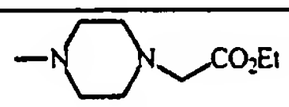
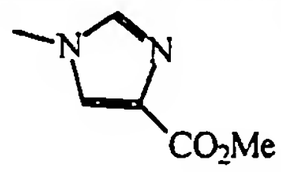
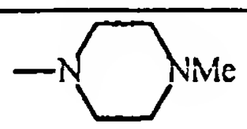
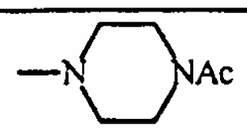
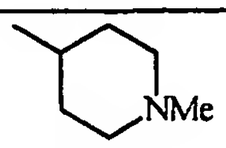
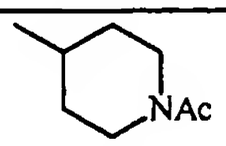
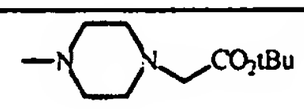
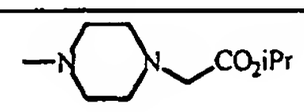
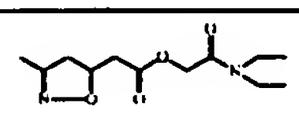
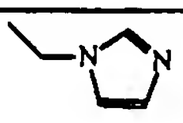


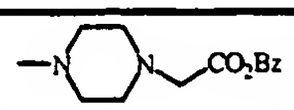
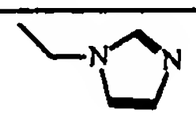
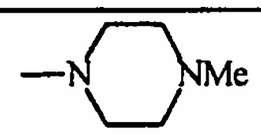
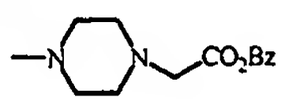
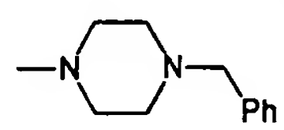
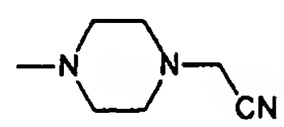
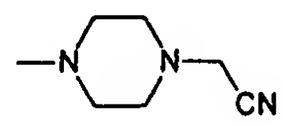
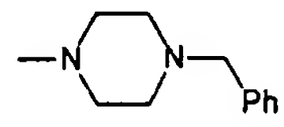
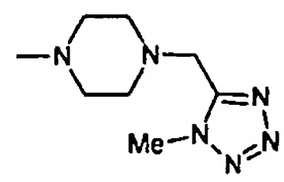
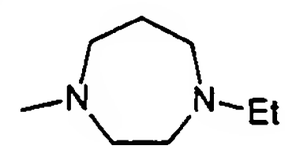
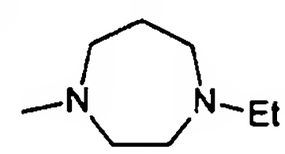
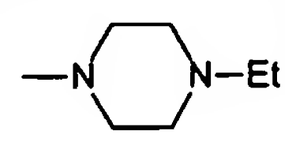
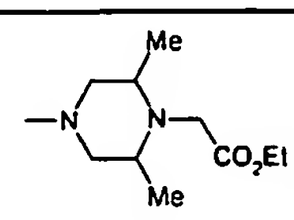
5 **4** **3**

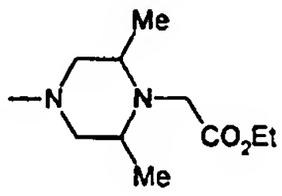
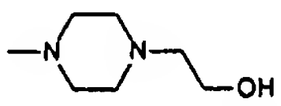
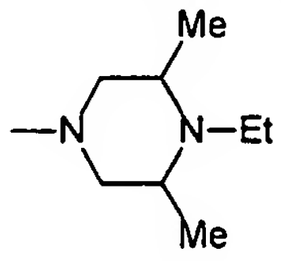
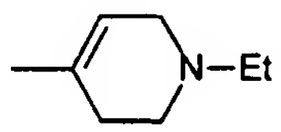
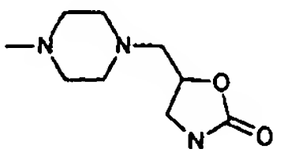
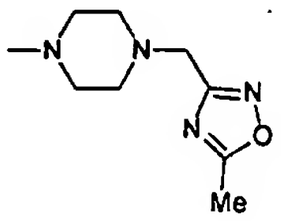
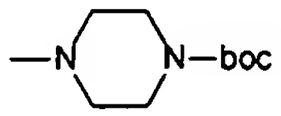
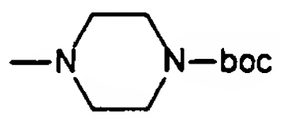
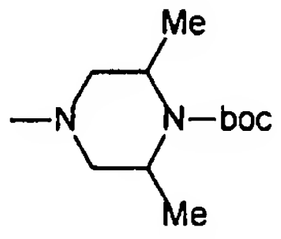
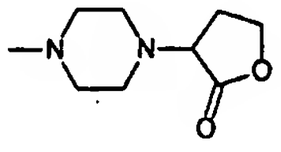
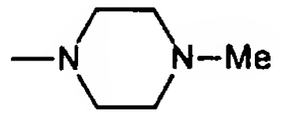
The nitroanilines of Table 3 were prepared by reaction of 4-chloro-3-nitrobenzoates **5** with substituted anilines (**4**), according to the above scheme as exemplified for compound **3a** below.

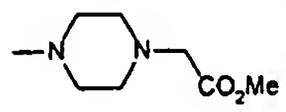
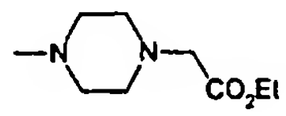
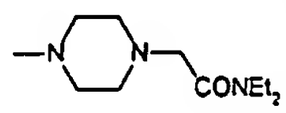
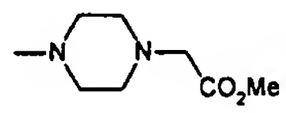
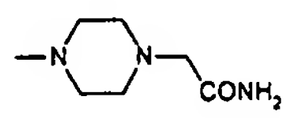
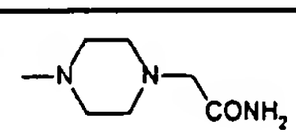
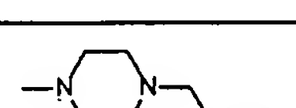
Table 3



Comp. No.	R_1	R_2	Starting materials	Yield (%)
3a	$MeO(CH_2)_2$		**4a, 5a**	43
3b	$MeO(CH_2)_2$		**4b, 5a**	67
3c	$MeO(CH_2)_2$		**4c, 5a**	37
3d	$MeO(CH_2)_2$		**4d, 5a**	52
3e	$MeO(CH_2)_2$		**4e, 5a**	81
3f	$MeO(CH_2)_2$		**4f, 5a**	58
3g	$MeO(CH_2)_2$		**4g, 5a**	-
3h	$MeO(CH_2)_2$		**4h, 5a**	74
3i	$MeO(CH_2)_2$		**4i, 5a**	45
3j	$MeO(CH_2)_2$		**4j, 5a**	57
3k	Et		**4k, 5b**	63
3l	Me		**4l, 5c**	32

Comp. No.	R_1	R_2	Starting materials	Yield (%)
3m	Me		**4d, 5c**	88
3n	$MeS(CH_2)_2$		**4l, 5d**	16
3o	$MeS(CH_2)_2$		**4e, 5d**	78
3p	$Me_2N(CH_2)_2$		**4d, 5e**	63
3p	$Me_2N(CH_2)_2$		**4d, 5e**	63
3r	$MeO(CH_2)_2$		**4s, 5a**	65
3s	Me		**4t, 5c**	53
3t	$MeO(CH_2)_2$		**4t, 5a**	74
3u	Me		**4s, 5c**	65
3w	$MeO(CH_2)_2$		**4u, 5a**	37
3x	$MeO(CH_2)_2$		**4v, 5a**	100
3y	Me		**4v, 5c**	100
3z	$MeO(CH_2)_2$		**4x, 5a**	100
3aa	$MeO(CH_2)_2$		**4y, 5a**	61

Comp. No.	R_1	R_2	Starting materials	Yield (%)
3bb	Me		**4y, 5c**	33
3cc	$HO(CH_2)_2$		**4z, 5f**	90
3dd	$MeO(CH_2)_2$		**4aa, 5a**	100
3ee	$MeO(CH_2)_2$		**4bb, 5a**	70
3ff	$MeO(CH_2)_2$		**4cc, 5a**	50
3gg	$MeO(CH_2)_2$		**4dd, 5a**	71
3hh	Me		**4ee, 5c**	38
3ii	$MeO(CH_2)_2$		**4ee, 5a**	69
3kk	$MeO(CH_2)_2$		**4ff, 5a**	89
3ll	$MeO(CH_2)_2$		**4gg, 5a**	75
3nn	$HO(CH_2)_2$		**4e, 5f**	59

Comp. No.	R_1	R_2	Starting materials	Yield (%)
3oo	$HO(CH_2)_2$		**5f**	56
3pp	$HO(CH_2)_2$		**4b, 5f**	27
3qq	$MeO(CH_2)_2$		**4ii, 5a**	24
3rr	$MeO(CH_2)_2$		**5a**	53
3ss	$MeO(CH_2)_2$		**4jj, 5a**	21
3uu	$HO(CH_2)_2$		**4jj, 5f**	82
3vv	$HO(CH_2)_2$		**4ii, 5f**	41

2-Methoxyethyl 3-nitro-4-(3-(1-ethoxycarbonyl-4-piperazinylmethyl)-phenylamino)-benzoate **3a**. A mixture of **5a** (0.94 g; 3.62 mmol), **4a** (1.0 g; 3.83 mmol) and triethylamine (0.53 ml; 3.80 mmol) in NMP (10 ml) was heated to 110°C overnight. The cooled mixture was partitioned between water and ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column-chromatography on silica gel using a mixture of ethyl acetate and petroleum ether (1:1 v/v) as the eluent. Yield: 0.75 g (43%).

The following compound were prepared in analogy with Compound **3a**:

2-Methoxyethyl 3-nitro-4-(3-(1-(ethoxy-carbonyl-methyl)-4-piperazinylmethyl)-phenylamino)-benzoate (**3b**) from **4b** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(4-methoxycarbonyl-1-imidazolyl)-phenylamino)-benzoate (**3c**) from **4c** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(1-(benzyloxy-carbonyl-methyl)-4-piperazinyl)-phenylamino)-benzoate (**3d**) from **4d** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(1-methyl-4-piperazinyl)-phenylamino)-benzoate (**3e**) from **4e** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(1-acetyl-4-piperazinyl)-phenylamino)-benzoate (**3f**) from **4f** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(1-methyl-4-piperidyl)-phenylamino)-benzoate (**3g**) from **4g** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(1-acetyl-4-piperidyl)-phenylamino)-benzoate (**3h**) from **4h** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(1-(*t*-butoxy-carbonyl-methyl)-4-piperazinyl)-phenylamino)-benzoate (**3i**) from **4i** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(1-(*i*-propoxy-carbonyl-methyl)-4-piperazinyl)-phenylamino)-benzoate (**3j**) from **4j** and **5a**.

(N,N-Diethylcarbamoyl)methyl 2-(3-(3-[N-(4-ethoxycarbonyl-3-nitrophenyl)-amino]-phenyl)-4,5-dihydroisoxazol-5-yl)-acetate (**3k**) from **4k** and **5b**.

Methyl 3-nitro-4-(3-(1-imidazolylmethyl)-phenylamino)-benzoate (**3l**) from **4l** and **5c**.

2-(Methylthio)-ethyl 3-nitro-4-(3-(1-imidazolylmethyl)-phenylamino)-benzoate (**3n**) from **4l** and **5d**.

2-(Methylthio)-ethyl 3-nitro-4-(3-(4-methyl-1-piperazinyl)-phenylamino)-benzoate (**3o**) from **4l** and **5d**.

2-Methoxyethyl 3-nitro-4-(3-(4-benzyl-1-piparazinyl)-phenylamino)-benzoate (**3r**) from **4s** and **5a**.

Methyl 3-nitro-4-(3-(4-(cyanomethyl)-1-piparazinyl)-phenylamino)-benzoate (**3s**) from **4t** and **5c**.

2-Methoxyethyl 3-nitro-4-(3-(4-(cyanomethyl)-1-piparazinyl)-phenylamino)-benzoate (**3t**) from **4t** and **5a**.

Methyl 3-nitro-4-(3-(4-benzyl-1-piparazinyl)-phenylamino)-benzoate (**3u**) from **4s** and **5c**.

2-Methoxyethyl 3-nitro-4-(3-(4-((1-methyl-5-tetrazolyl)methyl)-1-piparazinyl)-phenylamino)-benzoate (**3w**) from **4u** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(4-ethyl-1-homopiparazinyl)-phenylamino)-benzoate (**3x**) from **4v** and **5a**.

Methyl 3-nitro-4-(3-(4-ethyl-1-homopiparazinyl)-phenylamino)-benzoate (**3y**) from **4v** and **5c**.

2-Methoxyethyl 3-nitro-4-(3-(4-ethyl-1-piparazinyl)-phenylamino)-benzoate (**3z**) from **4v** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(4-ethoxycarbonylmethyl-3,5-dimethyl-1-piparazinyl)-phenylamino)-benzoate (**3aa**) from **4y** and **5a**.

Methyl 3-nitro-4-(3-(4-ethoxycarbonylmethyl-3,5-dimethyl-1-piparazinyl)-phenylamino)-benzoate (**3bb**) from **4y** and **5c**.

2-Hydroxyethyl 3-nitro-4-(3-(4-ethyl-3,5-dimethyl-1-piparazinyl)-phenylamino)-benzoate (**3dd**) from **4aa** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(1-ethyl-1,2,5,6-tetrahydropyridin-4-yl)-phenylamino)-benzoate (**3ee**) from **4bb** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(2-oxo-oxazolidin-5-yl)methyl)-phenylamino)-benzoate (**3ff**) from **4cc** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(4-((5-methyl-3-oxadiazolyl)methyl)-1-piparazinyl)-phenylamino)-benzoate (**3gg**) from **4dd** and **5a**.

Methyl 3-nitro-4-(3-(4-*boc*-piperazin-1-yl)-phenylamino)-benzoate (**3hh**) from **4ee** and **5c**.

2-Methoxyethyl 3-nitro-4-(3-(4-*boc*-piperazin-1-yl)-phenylamino)-benzoate (**3ii**) from **4ee** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(4-*boc*-3,5-dimethylpiperazin-1-yl)-phenylamino)-benzoate (**3kk**) from **4ff** and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(4-(2-oxotetrahydrofuran-3-yl)-1-piperazinyl)-phenylamino)-benzoate (**3ll**) from **4gg** and **5a**.

2-Hydroxyethyl 3-nitro-4-(3-(4-methyl-1-piparazinyl)-phenylamino)-benzoate (**3nn**) from **4e** and **5f**.

2-Hydroxyethyl 3-nitro-4-(3-(4-methoxycarbonylmethyl-1-piparazinyl)-phenylamino)-benzoate (**3oo**) from methyl 3-nitro-4-chlorobenzoate and **5f**.

2-Hydroxyethyl 3-nitro-4-(3-(4-ethoxycarbonylmethyl-1-piparazinyl)-phenylamino)-benzoate (**3pp**) from **4b** and **5f**.

2-Methoxyethyl 3-nitro-4-(3-(4-(N,N-diethylcarbamoylmethyl)-piperazin-1-yl)-phenylamino)-benzoate (**3qq**) from **4ii** and **5a**.

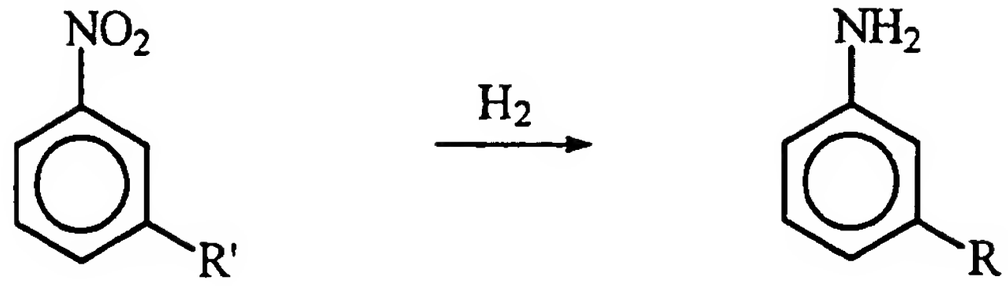
2-Methoxyethyl 3-nitro-4-(3-(4-methoxycarbonylmethyl-1-piparazinyl)-phenylamino)-benzoate (**3rr**) from methyl 3-nitro-4-chlorobenzoate and **5a**.

2-Methoxyethyl 3-nitro-4-(3-(4-(carbamoylmethyl)-piperazin-1-yl)-phenylamino)-benzoate (**3ss**) from **4jj** and **5a**.

2-Hydroxyethyl 3-nitro-4-(3-(4-(carbamoylmethyl)-piperazin-1-yl)-phenylamino)-benzoate (**3tt**) from **4jj** and **5f**.

2-Hydroxyethyl 3-nitro-4-(3-(4-(N,N-diethylcarbamoylmethyl)-piperazin-1-yl)-phenylamino)-benzoate (**3uu**) from **4ii** and **5f**.

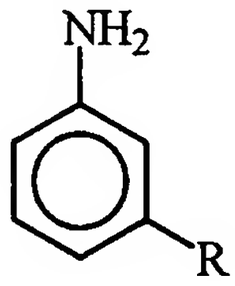
Example 4

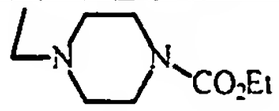
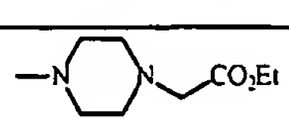
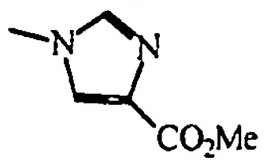
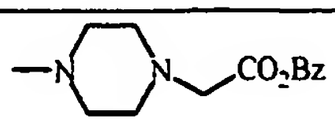
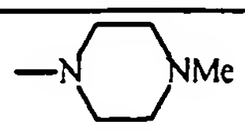
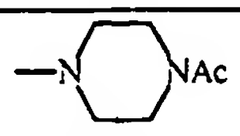
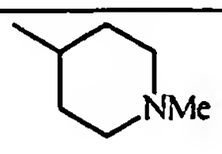
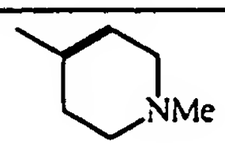


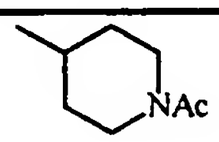
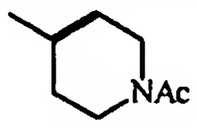
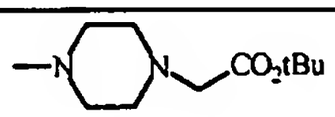
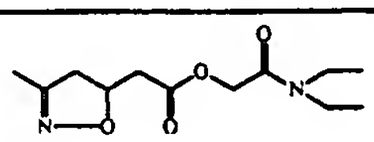
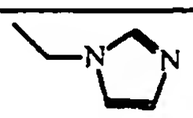
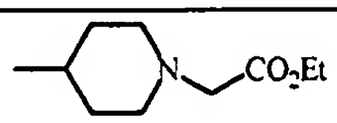
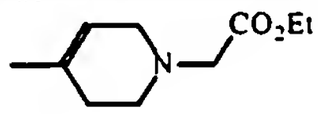
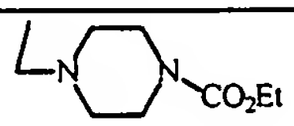
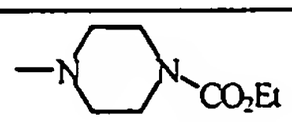
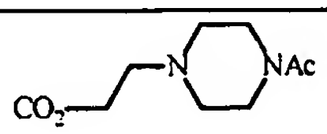
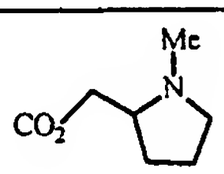
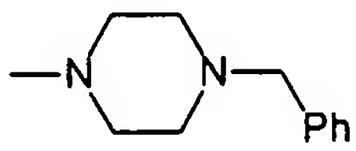
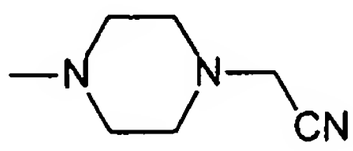
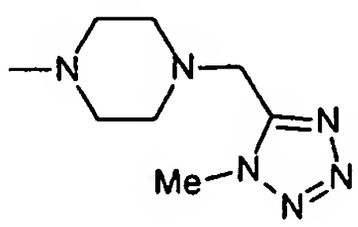
6 **4**

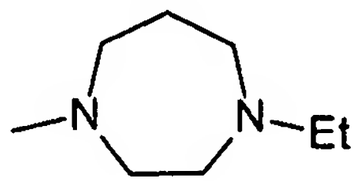
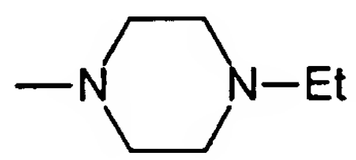
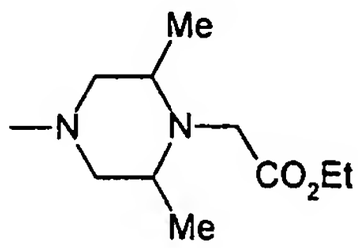
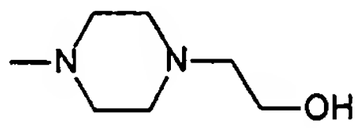
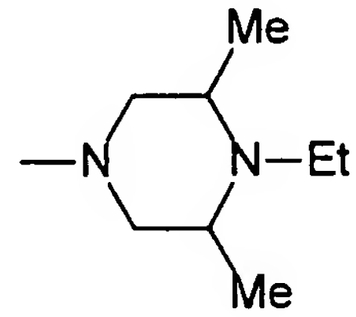
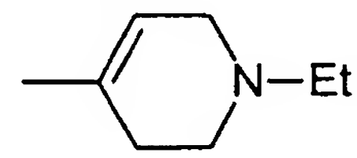
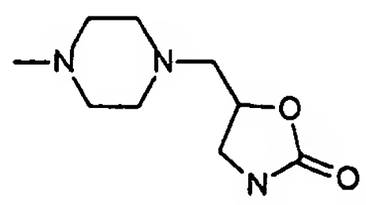
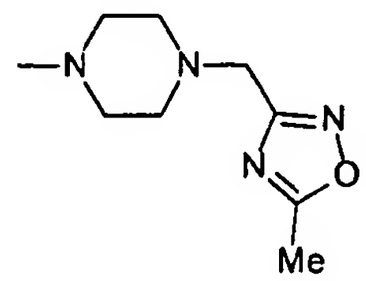
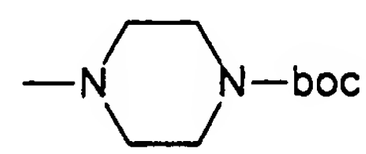
The substituted anilines of Table 4 were prepared by hydrogenation of the corresponding nitro compounds (**6**) as exemplified by compound **4a** below.

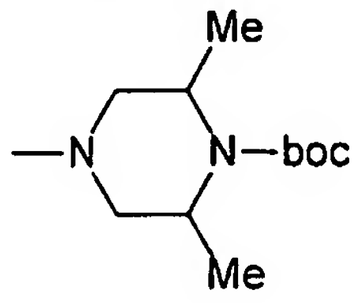
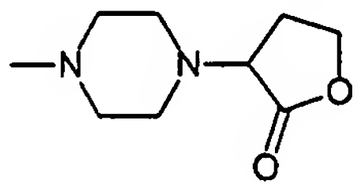
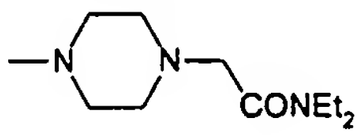
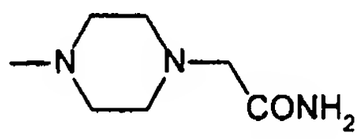
Table 4



Comp. No.	R	Starting material	R'	Preparation of starting material
4a		**6a**	R	Example 6a
4b		**6b**	R	Example 6b
4c		**6c**	R	Example 6c
4d		**6d**	R	Example 6d
4e		**6e**	R	Example 6e
4f		**6f**	R	Example 6f
4g		**6g**		Example 6g

Comp. No.	R	Starting material	R'	Preparation of starting material
4h		6h		Example 6h
4i		6i	R	Example 6b
4j		6j	R	Example 6b
4k		6k	R	Example 6k
4l		6l	R	Example 6l
4m		6m	R	Example 6m
4n		6n		Example 6n
4o		6o	R	Example 6o
4p		6p	R	Example 6p
4q		6q	R	Example 6q
4r		6r	R	Example 6r
4s		6s	R	Example 6b
4t		6t	R	Example 6b
4u		6u	R	Example 6u

Comp. No.	R	Starting material	R'	Preparation of starting material
4v		**6v**	R	Example 6b
4x		**6x**	R	Example 6b
4y		**6y**	R	Example 6b
4z		**6z**	R	Example 6b
4aa		**6aa**	R	Example 6b
4bb		**6bb**	R	Example 6g
4cc		**6cc**	R	Example 6b
4dd		**6dd**	R	Example 6b
4ee		**6ee**	R	Example 6b

Comp. No.	R	Starting material	R'	Preparation of starting material
4ff		**6ff**	R	Example 6b
4gg		**6gg**	R	Example 6b
4ii		**6ii**	R	Example 6b
4jj		**6jj**	R	Example 6b

1-Ethoxycarbonyl-4-(3-aminobenzyl)-piperazine **4a**. To a solution of **6a** (2.2 g; 7.5 mmol) in abs. ethanol (50 ml) was added palladium catalyst (100 mg, 5% Pd on activated carbon) and the mixture was hydrogenated at ambient pressure until the hydrogen uptake had ceased. Filtration through celite and evaporation of solvent left **4a**, quantitatively.

The following compound were prepared in analogy with Compound **4a**:

Ethyl 2-(4-(3-aminophenyl)-1-piperazinyl)-acetate (**4b**) from **6b**.

Methyl 1-(3-aminophenyl)-4-imidazolecarboxylate (**4c**) from **6c**.

Benzyl 2-(4-(3-aminophenyl)-1-piperazinyl)-acetate (**4d**) from **6d**. PtO_2 was used as the catalyst.

3-(4-Methyl-1-piperazinyl)-aniline (**4e**) from **6e**.

3-(4-Acetyl-1-piperazinyl)-aniline (**4f**) from **6f**.

3-(1-Methyl-4-piperidyl)-aniline (**4g**) from **6g**.

3-(1-Acetyl-4-piperidyl)-aniline (**4h**) from **6h**.

t-Butyl 2-(4-(3-aminophenyl)-1-piperazinyl)-acetate (**4i**) from **6i**.

i-Propyl 2-(4-(3-aminophenyl)-1-piperazinyl)-acetate (**4j**) from **6j**.

(N,N-Diethylcarbamoyl)-methyl 2-(3-(3-aminophenyl)-4,5-dihydroisoxazol-5-yl)-acetate (**4k**) from **6k**.

1-[(3-aminophenyl)-methyl]-imidazole (**4l**) from **6l**.

Ethyl 2-(4-[(3-aminophenyl)-methyl]-1-piperazinyl)-acetate (**4m**) from **6m**.

Ethyl 2-(4-(3-aminophenyl)-1-piperidyl)-acetate (**4n**) from **6n**.

Ethyl 2-(4-(3-aminophenyl)-methyl)-1-piperidyl)-acetate (**4o**) from **6o**.

Ethyl 2-(4-(3-aminophenyl)-1-piperazinyl)-acetate (**4p**) from **6p**.

2-(4-Acetyl-1-piperazinyl)-ethyl 3-aminobenzoate (**4q**) from **6q**. THF was used as solvent.

1-Methyl-2-pyrrolidylmethyl 3-aminobenzoate (**4r**) from **6r**. THF was used as solvent.

3-(4-benzyl-1-piperazinyl)-aniline (**4s**) from **6s**. PtO_2 was used as the catalyst.

2-(4-(3-aminophenyl)-1-piperazinyl)-acetonitril (**4t**) from **6t**.

3-(4-((1-methyltetrazol-5-yl)methyl)-1-piperazinyl)-aniline (**4u**) from **6u**. PtO_2 was used as the catalyst.

3-(4-ethyl-1-homopiperazinyl)-aniline (**4v**) from **6v**.

3-(4-ethyl-1-piperazinyl)-aniline (**4x**) from **6x**.

3-(4-ethoxycarbonylmethyl-3,5-dimethyl-1-piperazinyl)-aniline (**4y**) from **6y**.

3-(4-(2-hydroxyethyl)-1-piperazinyl)-aniline (**4z**) from **6z**.

3-(4-ethyl-3,5-dimethyl-1-piperazinyl)-aniline (**4aa**) from **6aa**.

3-(4-(2-oxo-oxazolidin-5-yl)methyl)-1-piperazinyl)-aniline (**4cc**) from **6cc**.

3-(4-(5-methyloxadiazol-3-yl)methyl)-1-piperazinyl)-aniline (**4dd**) from **6dd**.

3-(4-*boc*-1-piperazinyl)-aniline (**4ee**) from **6ee**.

3-(4-*boc*-3,5-dimethyl-1-piperazinyl)-aniline (**4ff**) from **6ff**.

3-(4-(2-oxotetrahydrofuran-3-yl)-1-piperazinyl)-aniline (**4gg**) from **6gg**.

3-(4-methoxycarbonylmethyl-1-piperazinyl)-aniline (**4hh**) as described in WO 98/17651.

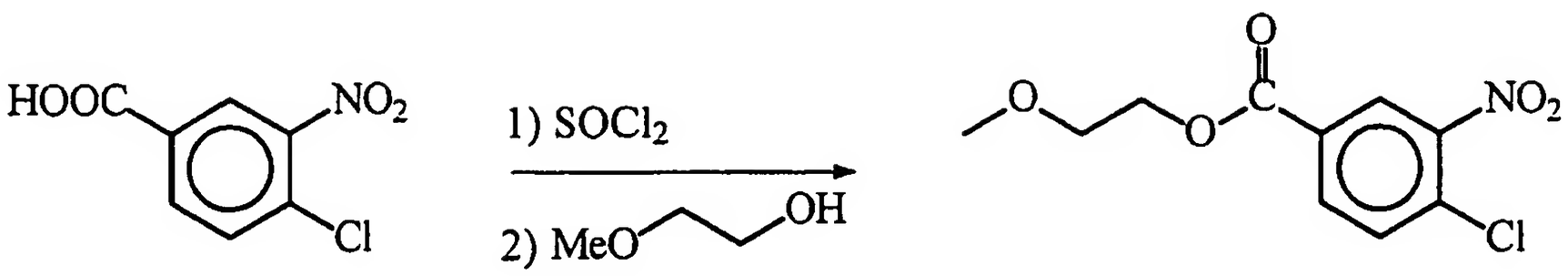
3-(4-((N,N-diethylcarbamoyl)methyl)-1-piperazinyl)-aniline (**4ii**) from **6ii**.

3-(4-(carbamoylmethyl)-1-piperazinyl)-aniline (**4jj**) from **6jj**.

Example 4a

3-(4-(1-ethyl-1,2,5,6-tetrahydropyridin-4-yl)-1-piperazinyl)-aniline (**4bb**). A mixture of **6bb** (Example 6g) (0.85 g; 3.66 mmol), sodium sulfide nonahydrate (2.64 g; 11.0 mmol) and ammonium chloride (0.58 g; 10.8mmol) in abs. ethanol (25 ml) was heated to reflux for 4 hours. The cooled mixture was poured into ice-water and extracted with dichloromethane. The extract was dried over magnesium sulphate, filtered and evaporated to leave **4bb**. Yield: 0.60 g (81%).

Example 5



2-Metyhoxyethyl 4-chloro-3-nitrobenzoate **5a**. A mixture of 4-chloro-3-nitrobenzoic acid (10.0 g; 49.6 mmol) and thionylchloride (50 ml) was heated to reflux overnight. The excess of thionylchloride was removed by evaporation and 2-methoxyethanol (50 ml) was added. The resulting mixture was stirred at 80°C for 4 hours. The cooled solution was diluted with water (500 ml) and extracted with ethyl acetate (2 × 100 ml). The organic extract was dried over magnesium sulphate and concentrated under reduced pressure. Trituration of the residue with petroleum ether left **5a** (8.0 g; 62%) as a low melting solid (Mp. 33-35°C).

The following compound were prepared in analogy with Compound **5a**:

Ethyl 4-chloro-3-nitrobenzoate (**5b**);

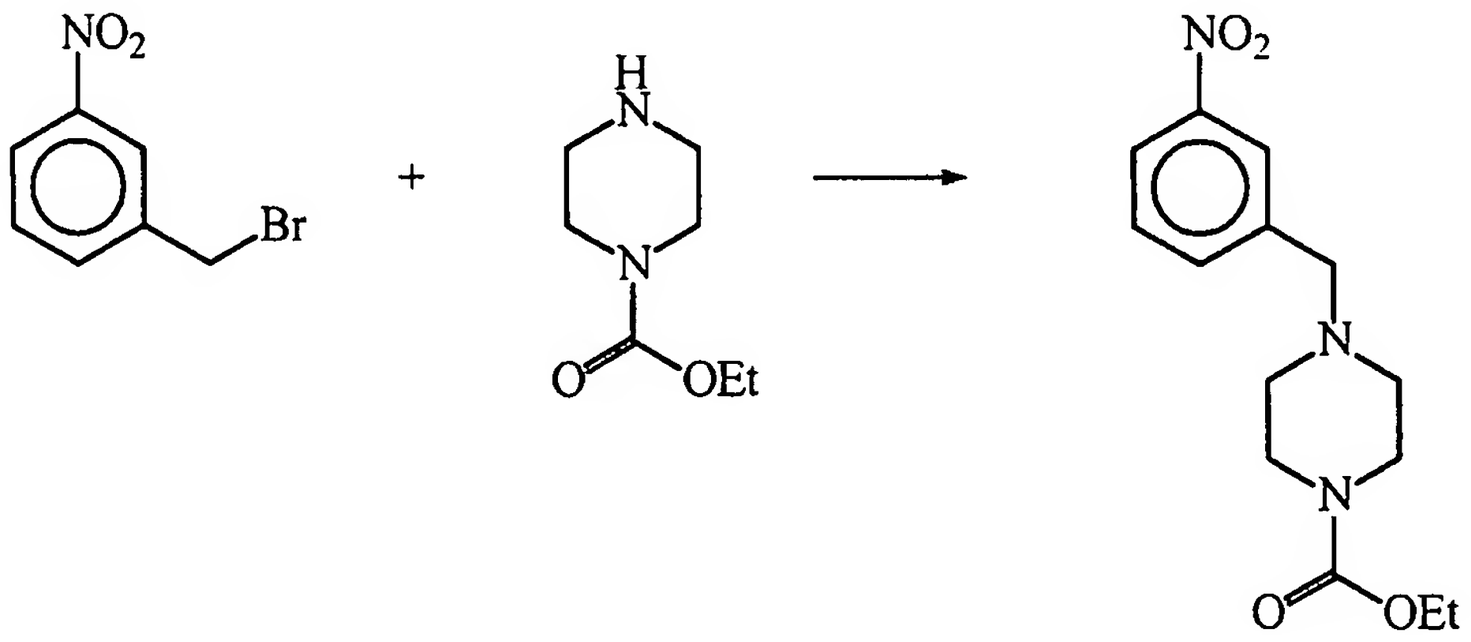
Methyl 4-chloro-3-nitrobenzoate (**5c**);

2-(Methylthio)ethyl 4-chloro-3-nitrobenzoate (**5d**);

2-(N,N-dimethylamino)ethyl 4-chloro-3-nitrobenzoate (**5e**); and

2-Hydroxyethyl 4-chloro-3-nitrobenzoate (**5f**).

Example 6a

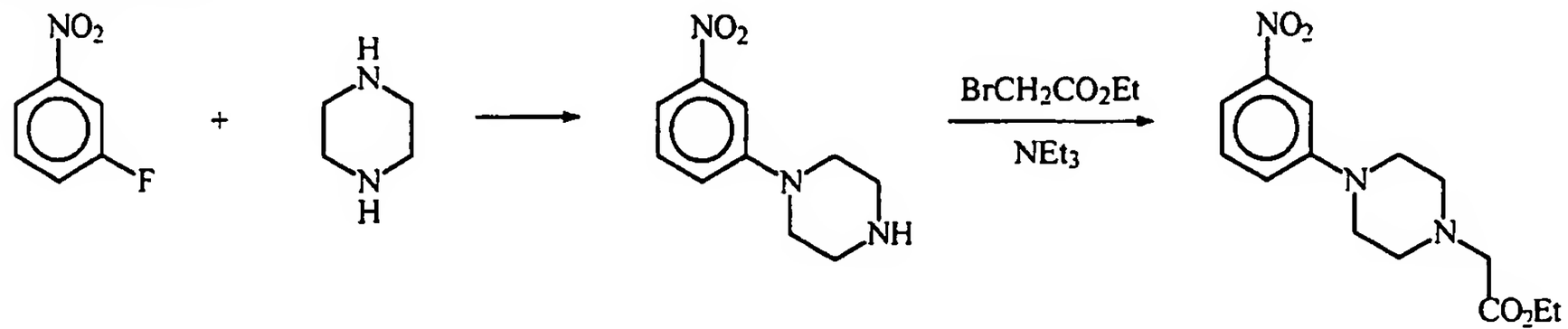


6a

1-Ethoxycarbonyl 4-(3-nitrobenzyl)-piperazine (**6a**). To a solution of 3-nitrobenzylbromide (2.2 g; 10.0 mmol) in NMP (5 ml) was added ethyl piperazine-1-carboxylate dropwise with stirring. At the end of the addition the temperature had reached 35°C. Triethylamine (1.39 ml) was added causing the temperature to rise to 40°C. The mixture was stirred for additionally 30 min. prior to dilution with diethyl ether (25 ml). The mixture was filtered and the filtrate was washed with water, dried over magnesium sulphate and concentrated under reduced pressure. The concentrate was

suspended in diethyl ether and filtered. The filtrate was diluted with ethyl acetate and extracted with diluted hydrochloric acid. The aqueous phase was rendered alkaline by addition of saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and evaporated to dryness to leave **6a** (1.72 g; 59%).

Example 6b



1-(3-Nitrophenyl)-piperazine. A suspension of 3-fluoronitrobenzene (23 ml; 0.21 mol) and piperazine (55.5 g; 0.64 mol) in anhydrous NMP (30 ml) was heated to 70°C for five days. The cooled mixture was diluted with water (250 ml) and extracted with dichloromethane. The combined extracts were dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column-chromatography on silica gel eluting subsequently with mixtures of ethyl acetate and methanol (4:1 v/v) and (1:1 v/v) to leave the desired product as oily crystals (30.7 g; 71%).

Ethyl 2-(4-(3-nitrophenyl)-1-piperazinyl)-acetate (**6b**). To a solution of 1-(3-nitrophenyl)piperazine (12.0 g; 58 mmol) in DMF (60 ml) was added sodium hydride (2.55 g; 64 mmol, 60% dispersion in mineral oil) in portions over 30 min. The mixture was kept under nitrogen. Ethyl 2-bromoacetate (7.1 ml; 64 mmol) was added, the mixture was stirred at ambient temperature for one hour and then poured into water (250 ml). The oily precipitate was filtered off, re-dissolved in ethyl acetate and washed with water. The organic phase was dried over magnesium sulphate and evaporated to dryness to leave **6b** (11.0 g; 65%).

The following compound were prepared in analogy with Compound **6b**:

Isopropyl 2-(4-(3-nitrophenyl)-1-piperazinyl)-acetate (**6j**) from 1-(3-nitrophenyl)piperazine and isopropyl 2-bromoacetate.

t-Butyl 2-(4-(3-nitrophenyl)-1-piperazinyl)-acetate (**6i**) from 1-(3-nitrophenyl)piperazine and *t*-butyl 2-bromoacetate.

1-(3-Nitrophenyl)-4-benzylpiperazine (**6s**) from 1-(3-nitrophenyl)piperazine and benzylchloride.

2-(1-(3-Nitrophenyl)-4-piperazinyl)-acetonitrile (**6t**) from 1-(3-nitrophenyl)piperazine and 2-bromoacetonitrile.

1-(3-Nitrophenyl)-4-ethylhomopiperazine (**6v**) from 1-(3-nitrophenyl)homopiperazine (prepared analogously to 1-(3-nitrophenyl)piperazine) and iodoethane.

1-(3-Nitrophenyl)-4-methylpiperazine (**6x**) from 1-(3-nitrophenyl)piperazine and iodomethane.

1-(3-Nitrophenyl)-4-ethoxycarbonylmethyl-3,5-dimethylpiperazine (**6y**) from 1-(3-nitrophenyl)-2,6-dimethylpiperazine (prepared analogously to 1-(3-nitrophenyl)piperazine) and ethyl 2-bromoacetate.

1-(3-Nitrophenyl)-4-(2-hydroxyethyl)-piperazine (**6z**) from 1-(3-nitrophenyl)piperazine and 2-bromoethanol.

1-(3-Nitrophenyl)-4-ethyl-3,5-dimethylpiperazine (**6aa**) from 1-(3-nitrophenyl)-2,6-dimethylpiperazine (prepared analogously to 1-(3-nitrophenyl)-piperazine) and iodoethane.

1-(3-Nitrophenyl)-4-((2-oxo-oxazolidin-5-yl)-methyl)-piperazine (**6cc**) from 1-(3- nitrophenyl)-piperazine and 5-chloromethyl-2-oxazolidinone.

1-(3-Nitrophenyl)-4-((5-methyloxadiazol-3-yl)-methyl)-piperazine (**6dd**) from 1-(3-nitrophenyl)piperazine and 3-chloromethyl-5-methyloxadizole.

1-(3-Nitrophenyl)-4-*boc*-piperazine (**6ee**) from 1-(3-nitrophenyl)-piperazine and Boc-anhydride.

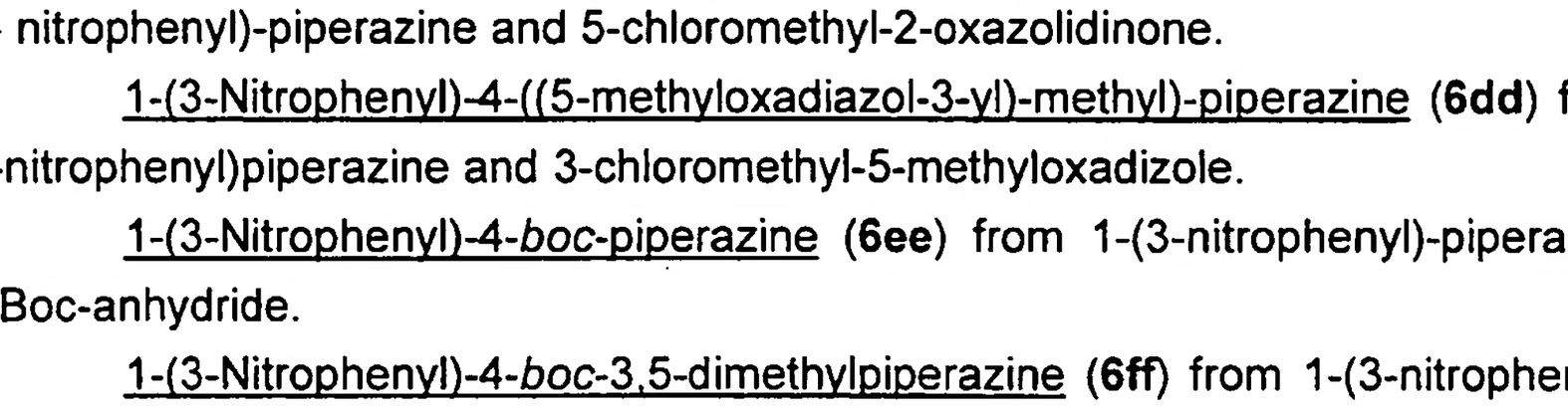
1-(3-Nitrophenyl)-4-*boc*-3,5-dimethylpiperazine (**6ff**) from 1-(3-nitrophenyl)-2,6-dimethylpiperazine (prepared analogously to 1-(3-nitrophenyl)-piperazine) and Boc-anhydride.

1-(3-Nitrophenyl)-4-(2-oxotetrahydrofuran-3-yl)-piperazine (**6gg**) from 1-(3-nitrophenyl)-piperazine and a-bromobutyrolactone.

1-(3-Nitrophenyl)-4-((N,N-diethylarbamoyl)-methyl)-piperazine (**6ii**) from 1-(3-nitrophenyl)-piperazine and 2-chloro-N,N-diethylacetamide.

1-(3-Nitrophenyl)-4-(carbamoylmethyl)-piperazine (**6jj**) from 1-(3-nitrophenyl)-piperazine and 2-chloroacetamide.

Example 6c

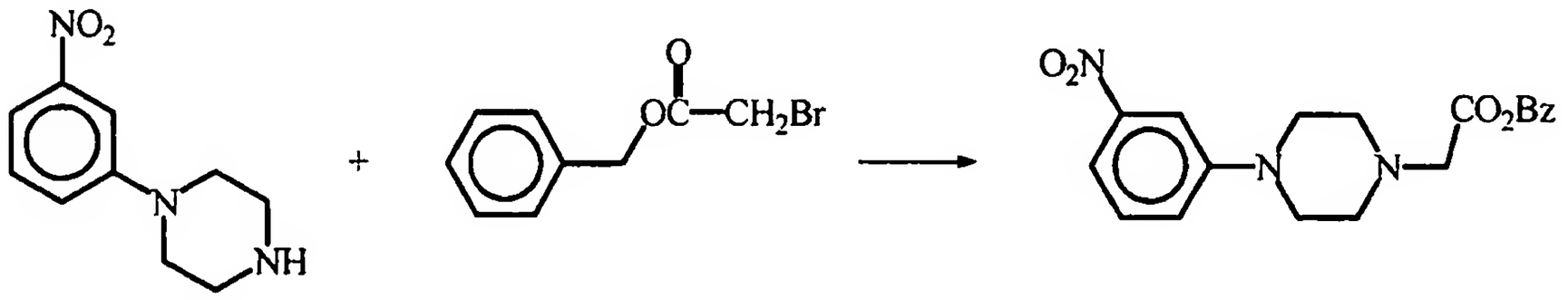


6c

Methyl 1-(3-nitrophenyl)-imidazole-4-carboxylate (**6c**). A mixture of 3-fluoronitrobenzene (1.78 ml; 16.7 mmol), methyl imidazole-4-carboxylate and

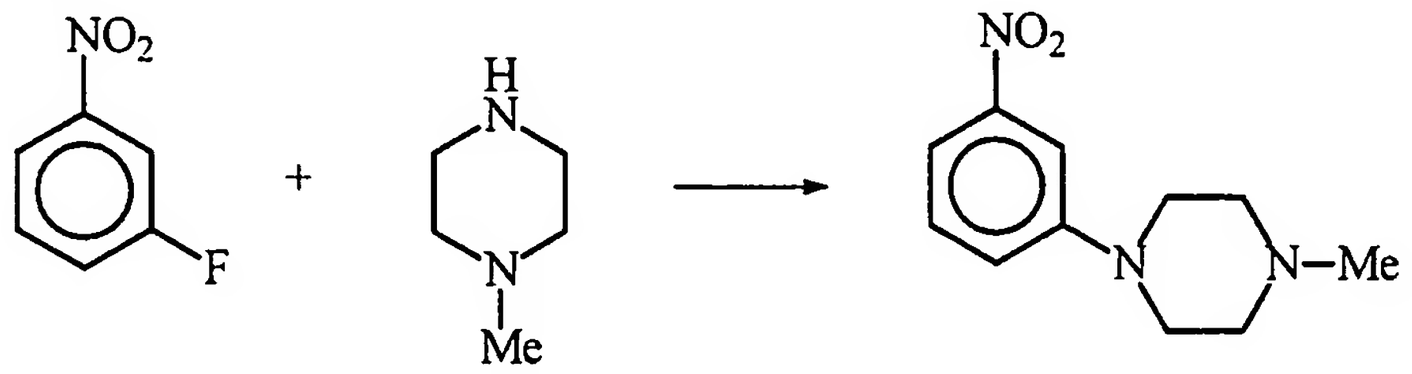
potassium carbonate (2.3 g; 16.7 mmol) in 10 ml NMP was heated to 120°C in a nitrogen atmosphere overnight. The cooled mixture was poured into water (100 ml), the precipitate was filtered off, washed with water and dried to yield **6c** (2.38 g; 58%).

Example 6d



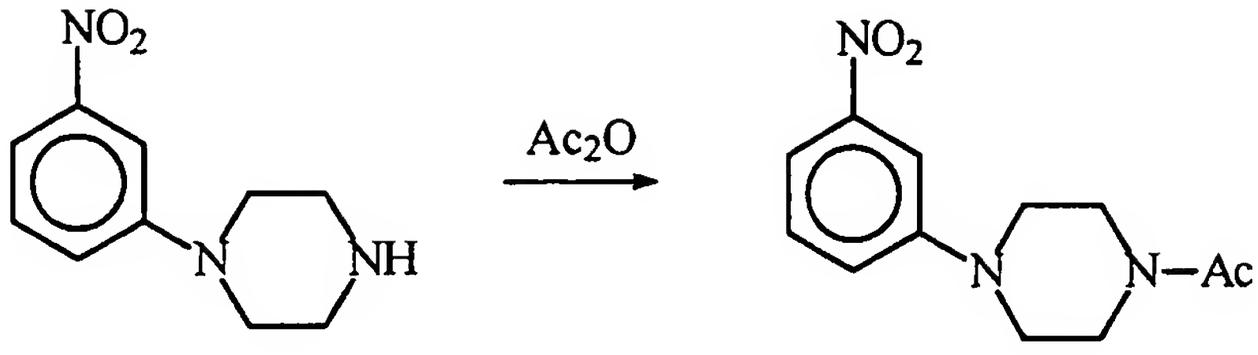
Benzyl 2-(4-(3-nitrophenyl)-1-piperazinyl)-acetate (**6d**). To a solution of 1-(3-nitrophenyl)piperazine (Example 6a) (10.0 g; 48.3 mmol) in anhydrous DMF (50 ml) was added sodium hydride (2.12 g, 60% dispersion in mineral oil; 53.1 mmol) in small portions. The mixture was stirred and benzyl 2-bromoacetate was added. The addition was extremely exothermic. The reaction mixture was left with stirring at ambient temperature overnight. The mixture was poured into water (200 ml) and extracted with ethyl acetate. The combined extracts were dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column-chromatography on silica gel using ethyl acetate as the eluent to yield **6c** (14.4 g; 84%).

Example 6e



1-(3-Nitrophenyl)-4-methylpiperazine (**6e**). A mixture of 3-fluoronitrobenzene (20 ml; 0.19 mol) and 1-methylpiperazine (40 ml; 0.36 mol) was heated to 120°C for a week. The cooled mixture was purified by column-chromatography on silica gel using a mixture of ethyl acetate and methanol (9:1 v/1) as the eluent. Yield: 33 g (79%).

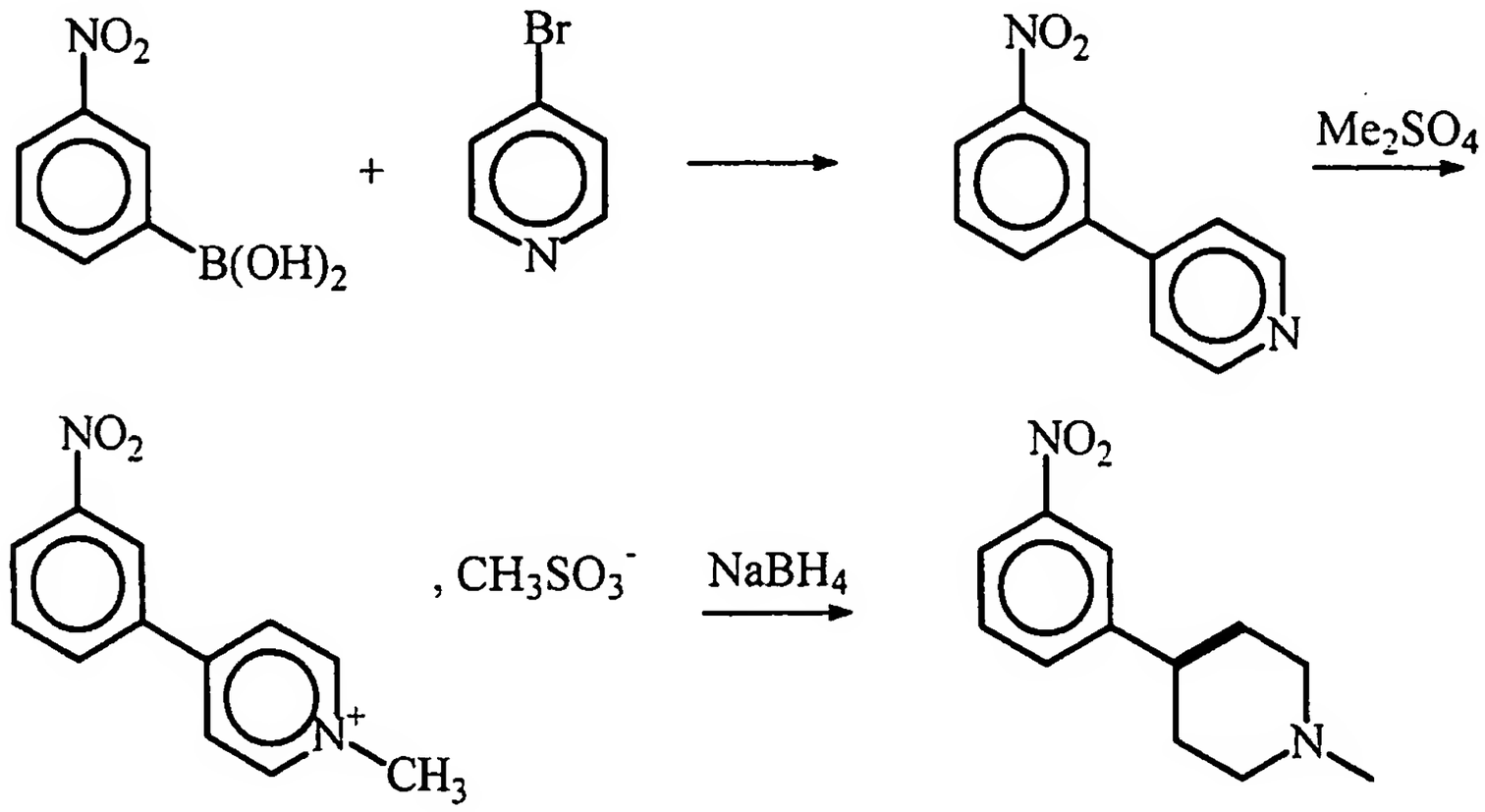
Example 6f



6f

1-Acetyl-4-(3-nitrophenyl)-piperazine (**6f**). A mixture of 1-(3-nitrophenyl)piperazine (Example 6a) (33.0 g; 0.16 mol) and acetic anhydride (130 ml) was stirred at ambient temperature overnight. The excess of acetic anhydride was removed by evaporation and saturated aqueous sodium carbonate was added to the residue with stirring. The precipitate was filtered off, washed with water and dried to leave **6f** (39 g; 98%).

Example 6g



6g

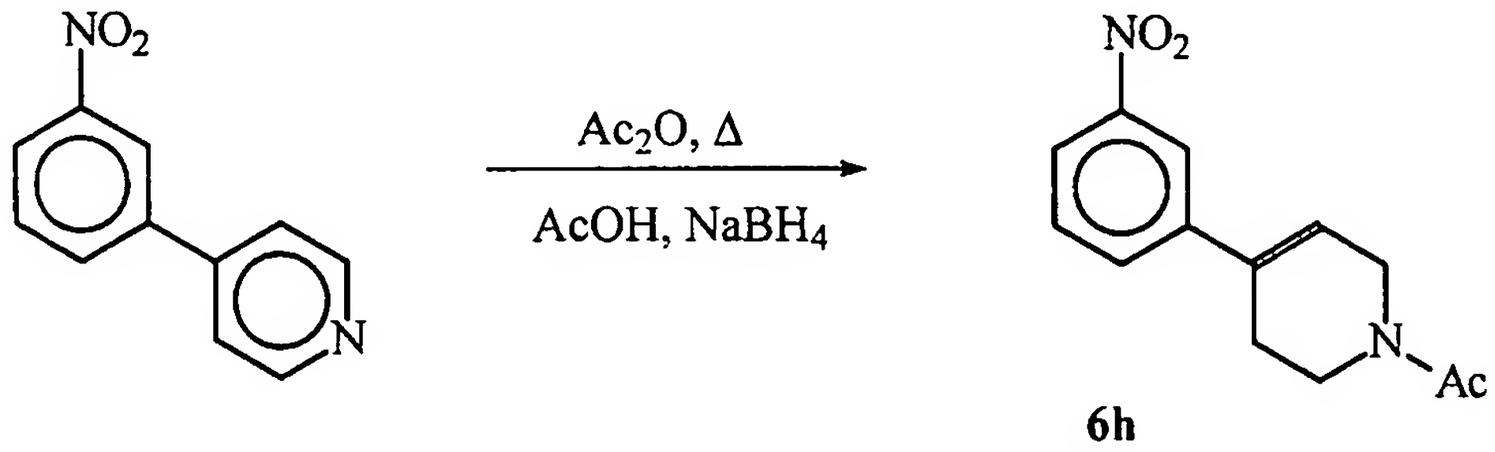
4-(3-Nitrophenyl)-pyridine. A mixture of 4-bromopyridine, hydrochloride (8.03; 41.3 mmol), 3-nitrophenylboronic acid (6.85 g; 41.0 mmol), potassium carbonate (34.2 g; 0.25 mol), 1,3-propandiol (14.9 ml; 0.21 mol) and tetrakis(triphenylphosphine)palladium (0.2 g) in a mixture of dimethoxyethane (80 ml) and water (40 ml) was stirred at 80°C in a nitrogen atmosphere overnight. The cooled mixture was diluted with ethyl acetate and filtered through celite. The filtrate was evaporated to dryness and water was added to the residue. Vigorously stirring caused the product to precipitate. The product was filtered off, washed with water, dried and subsequently washed with petroleum ether. Yield: 8.15 g (99%).

1-Methyl-4-(3-nitrophenyl)-pyridinium monomethyl-sulphate. A mixture of 4-(3-nitrophenyl)pyridine (4.0 g; 20 mmol) and dimethylsulphate (10 ml) was heated to 100°C for five days. The cooled mixture wad diluted with diethyl ether (50 ml) and stirred thoroughly. The mixture was decanted and the oily bottom layer was washed additionally three times with diethyl ether and once with ethanol to leave the crystalline product (2.9 g; 47%).

1-Methyl-4-(3-nitrophenyl)-1,2,5,6-tetrahydropyridine (**6g**). To a suspension of 1-methyl-4-(3-nitrophenyl)pyridinium monomethylsulphate (2.8 g; 9.03 mmol) in methanol (50 ml) was added sodium borohydride (0.68 g; 18.0 mmol) in portions over 30 min. Following the addition the mixture was stirred at ambient temperature overnight. The mixture was diluted with water (200 ml) and extracted with ethyl acetate (2 × 100 ml). The combined extracts were washed with brine, dried over magnesium sulphate and evaporated to dryness. Trituration of the residue with diethyl ether left the crystalline product (1.7 g; 86%).

1-Ethyl-4-(3-nitrophenyl)-1,2,5,6-tetrahydropyridine (**6bb**) was prepared analogously by alkylation with iodoethane.

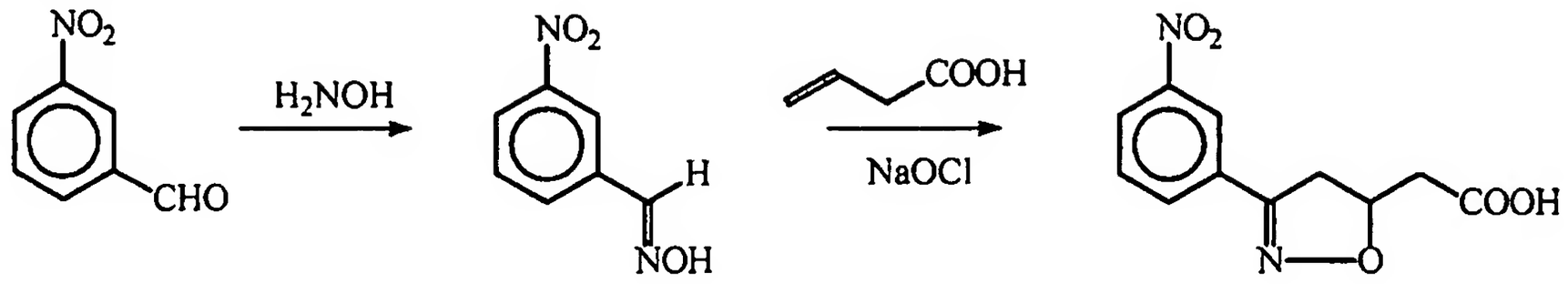
Example 6h



6h

1-Acetyl-4-(3-nitrophenyl)-1,2,5,6-tetrahydropyridine (**6h**). To a mixture of 4-(3-nitrophenyl)pyridine (Example 6g) (4.0 g; 20.0 mmol) and acetic anhydride (20 ml) in glacial acetic acid (30 ml) was added sodium borohydride (1.51 g; 40.0 mmol) in portions over one hour. The resulting mixture was stirred at ambient temperature for five days and then poured into ice-water. The mixture was extracted with ethyl acetate, the organic phase was washed with water, dried over magnesium sulphate and concentrated under reduced pressure. The residue was eluted through silica gel with ethyl acetate to yield **6h** (1.29 g; 26%).

Example 6k



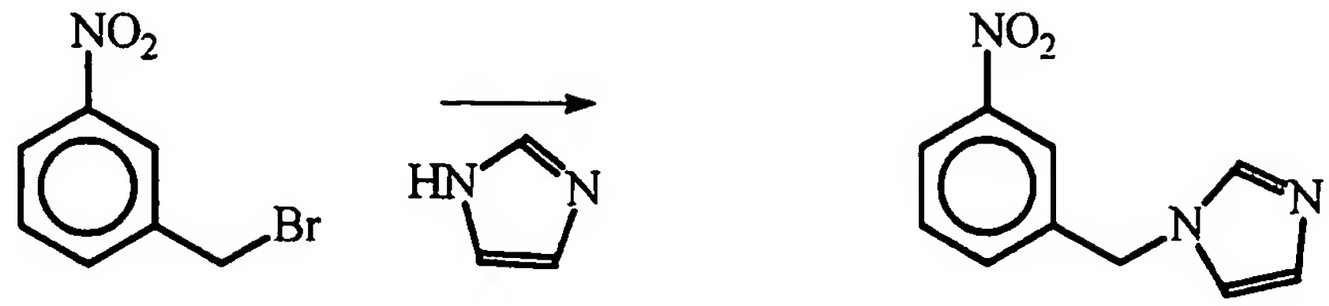
6k

3-Nitrobenzaldehyde oxime (**6k$_2$**). To a solution of 3-nitrobenzaldehyde (5.0 g; 33.1 mmol) in abs. ethanol (40 ml) was added hydroxylamine, hydrochloride (3.45 g; 49.6 mmol) and the resulting suspension was heated to reflux overnight. The cooled mixture was poured into water (100 ml) and the product was filtered off and dried. Yield: 4.5 g (82%).

2-(3-(3-Nitrophenyl)-4,5-dihydroisoxazol-5-yl)-acetic acid. To a solution of **6k$_2$** (3.1 g; 18.8 mmol) in THF (30 ml) was added vinylacetic acid (3.41 ml; 56.4 mmol). An aqueous solution of sodium hypochlorite (47 ml; 0.2 M) was added dropwise keeping the temperature between 25-30°C. Following the addition the mixture was stirred at ambient temperature overnight. pH was adjusted to 4 by addition of aqueous citric acid and the mixture was extracted thrice with diethyl ether. The combined extracts were dried over sodium sulphate and concentrated under reduced pressure. The concentrate was purified by column-chromatography on silica gel using a mixture of ethyl acetate and methanol (9:1 v/v) as the eluent. Yield: 4.7 g (98%).

N,N-Diethylcarbamoylmethyl 2-(3-(3-nitrophenyl)-4,5-dihydroisoxazole-5-yl)-acetate (**6k**). A mixture of **6k$_2$** (4.6 g; 18.4 mmol), 2-chloro N,N-diethylacetamide (2.53 ml; 18.4 mmol), triethylamine (5.1 ml; 36.6 mmol) and a catalytic amount of sodium iodide in anhydrous DMF (25 ml) was stirred at ambient temperature overnight. The solvent was removed by evaporation under reduced pressure and the residue was partitioned between water and ethyl acetate. The organic phase was dried over sodium sulphate and concentrated under reduced pressure.

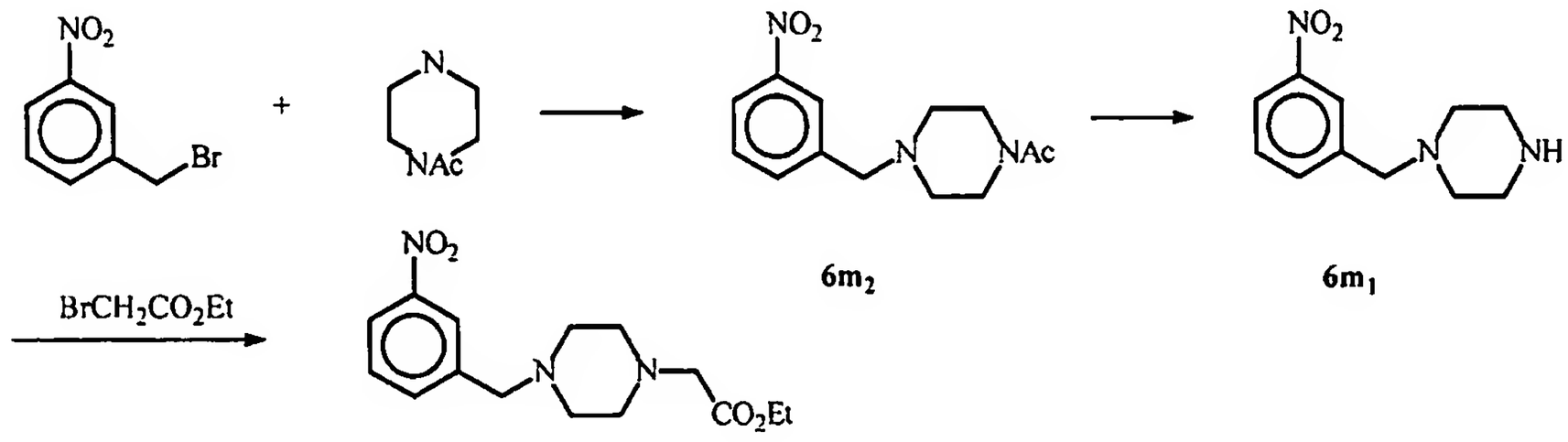
Example 6l



6l

1-(3-Nitrobenzyl)-imidazole (**6k**). A mixture of 3-nitrobenzylbromide (10 g; 46.3 mmol) and imidazole (6.3 g; 92.5 mmol) in NMP (10 ml) was stirred at 80°C overnight. The cooled mixture was poured into ice-water and rendered alkaline by addition of aqueous sodium hydroxide (4 M). The precipitate was filtered off, washed with water and dried to yield **6l** (6.9 g; 73%).

Example 6m



6m

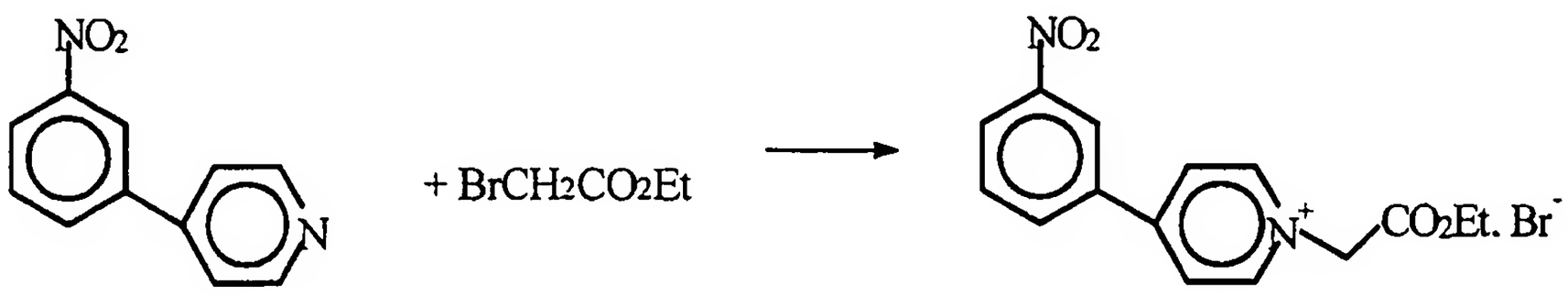
1-Acetyl-4-(3-nitrobenzyl)-piperazine (**6m$_2$**). To a solution of 1-acetylpiperazine (5.0 g; 39.0 mmol) in THF (50 ml) was added triethylamine (5.6 ml; 39.0 mmol) and 3-nitrobenzylbromide (8.4 g; 39.0 mmol). The mixture was stirred at ambient temperature for 1 hour and the solvent was removed by evaporation. The residue was partitioned between water and ethyl acetate. The organic phase was dried over sodium sulphate and evaporated under reduced pressure to leave **6m$_2$**, quantitatively.

1-(3-Nitrobenzyl)-piperazine (**6m$_1$**). To a solution of **6m$_2$** (10.2 g; 39.0 mmol) in dimethoxyethane (100 ml) was added aqueous sodium hydroxide (120 ml; 1 M) and the mixture heated to reflux overnight. The mixture was evaporated to dryness and the residue was extracted with a mixture of ethanol and dichloromethane (2:1 v/v). The extract was evaporated to dryness to leave **6m$_1$** (6.1 g; 71%).

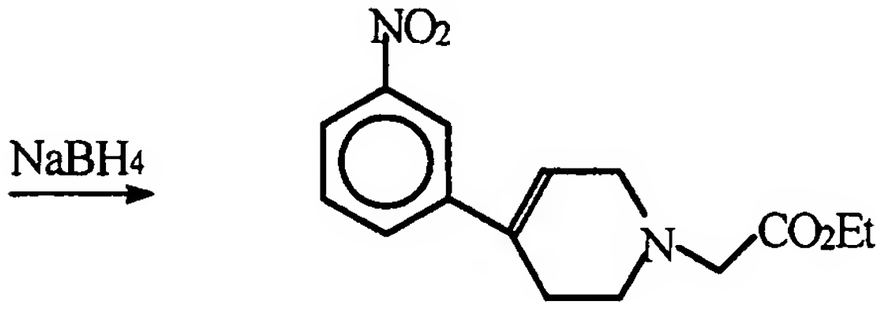
Ethyl 2-(4-(3-nitrobenzyl)-1-piperazinyl)-acetate (**6m**). To a solution of **6m$_1$** (2.5 g; 11.3 mmol) in anhydrous DMF (20 ml) was added sodium hydride (13.6 mmol; 0.54 g 60% dispersion in mineral oil) and ethyl 2-bromoacetate (1.25 ml; 11.3 mmol).

The exothermic reaction was completed in 15 min. The mixture was poured into ice-water and extracted with ethyl acetate. The organic extract was dried over sodium sulphate and evaporated to dryness to leave **6m** quantitatively.

Example 6n



6n1

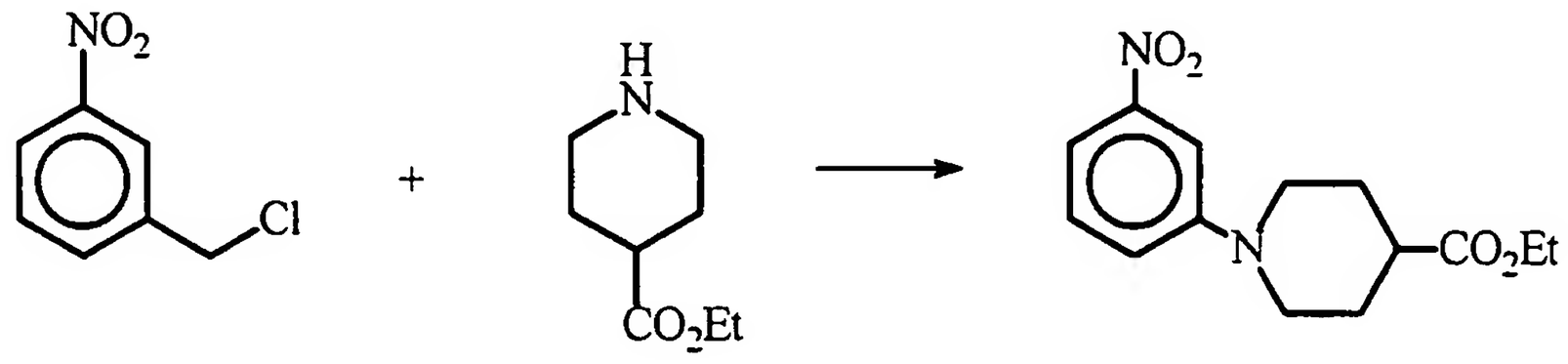


6n

1-(Ethoxy-carbonyl-methyl)-4-(3-nitrophenyl)-pyridinium bromide (**6n$_1$**). A mixture of 4-(3-nitrophenyl)pyridine (2.25 g; 11.3 mmol) and ethyl 2-bromoacetate (1.5 ml; 13.5 mmol) in THF (10 ml) was heated to reflux overnight. The cooled mixture was filtered and the crystalline product was washed with THF and dried to leave **6n$_1$** (3.49 g; 84%).

1-(Ethoxy-carbonyl-methyl)-4-(3-nitrophenyl)-1,2,5,6-tetrahydropyridine (**6n**). To a suspension of **6n$_1$** (2.90 g; 7.88 mmol) in abs. ethanol (50 ml) was added sodium borohydride (0.60 g; 15.9 mmol) in portions over 1 hour. The mixture was stirred at ambient temperature for two days, poured into ice-water and extracted with ethyl acetate. The extract was dried over sodium sulphate, concentrated and eluted through silica gel with ethyl acetate to yield **6n** (1.65 g; 72%).

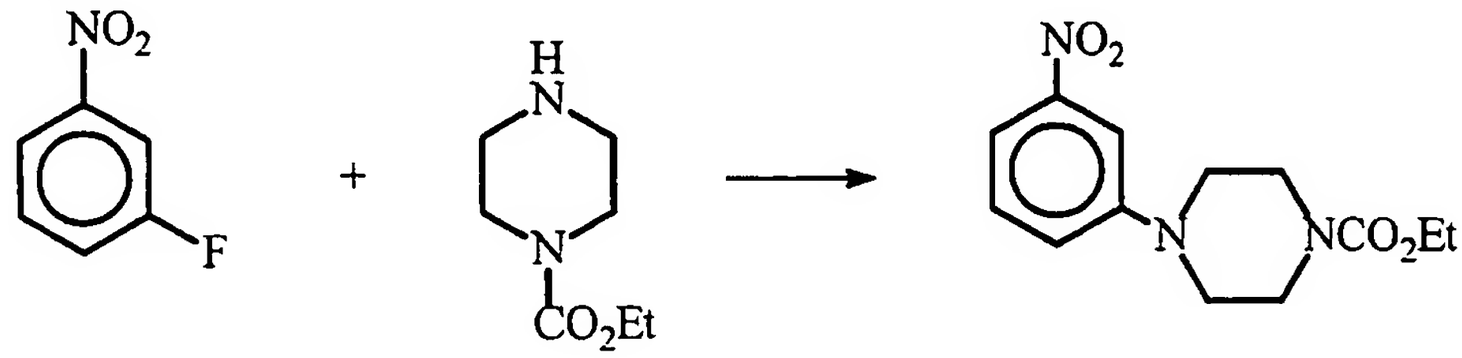
Example 6o



6o

Ethyl 1-(3-nitrophenyl)-piperidine-4-carboxylate (**6o**). To a solution of 3-nitrobenzylchloride (2.0 g; 11.7 mmol) and triethylamine (1.65 ml; 11.7 mmol) in NMP (3 ml) was added ethyl isonipecotate (1.8 ml; 11.7 mmol). The mixture was heated to 80°C overnight. The cooled mixture was poured into water and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulphate and evaporated to dryness to leave **6o**, quantitatively.

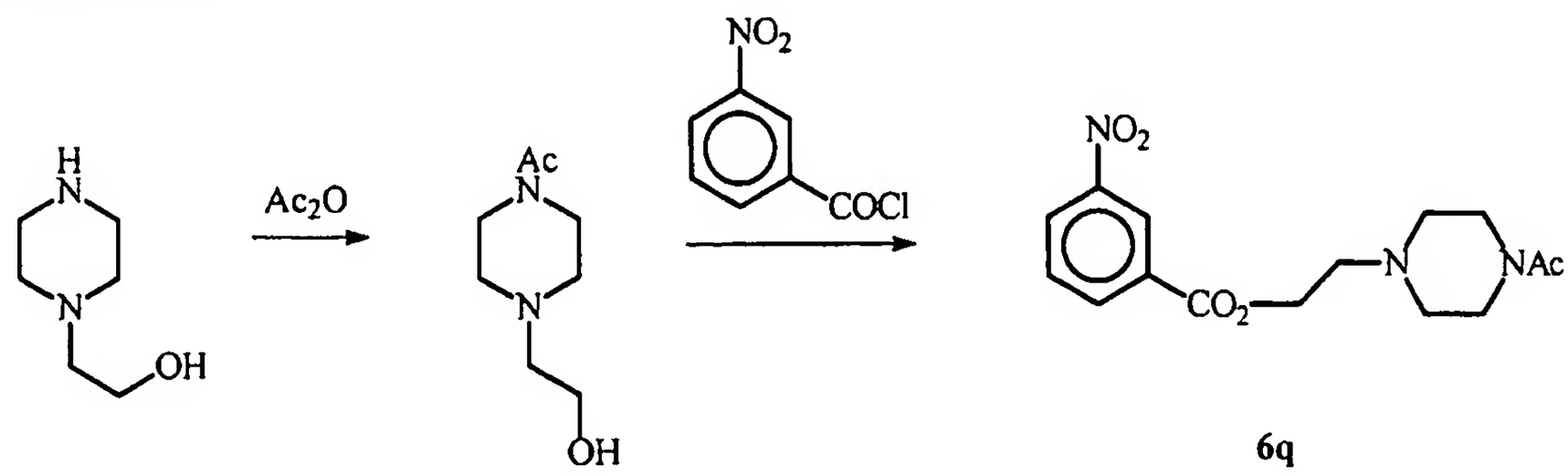
Example 6p



6p

1-Ethoxycarbonyl-4-(3-nitrophenyl)-piperazine (**6p**). To a solution of 3-fluoro-1-nitrobenzene (3.37 ml; 31.6 mmol) in NMP (5 ml) was added triethylamine (4.38 ml; 31.6 mmol) and ethyl 1-piperazinecarboxylate (4.63 ml; 31.6 mmol) and the mixture was heated to 120°C for five days. The cooled mixture was poured into ice-water and a small volume of ethanol was added. Vigorous stirring caused the product to precipitate. The product was filtered off, washed with petroleum ether and dried to leave **6p** (3.34 g; 38%).

Example 6q



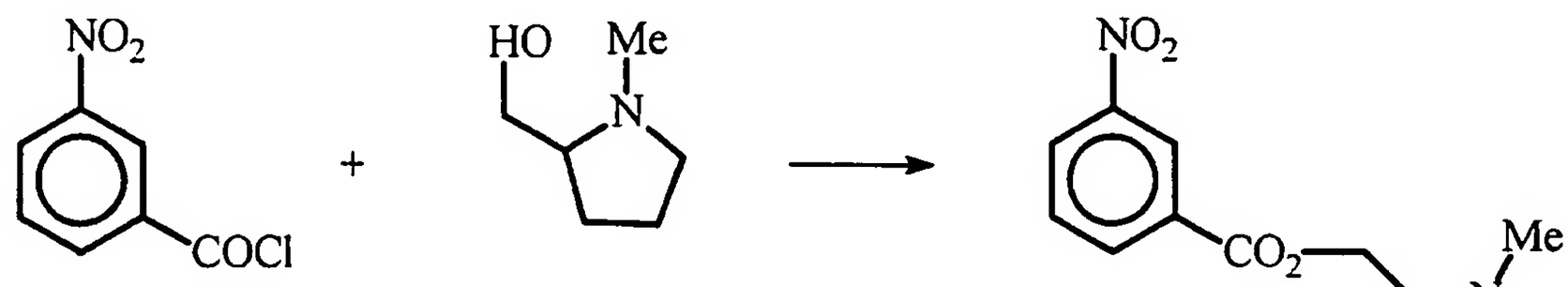
6q1 **6q**

1-Acetyl-4-(2-hydroxyethyl)-piperazine (**6q$_1$**). To a solution of 1-(2-hydroxyethyl)piperazine (5.5 ml; 42.3 mmol) in toluene (50 ml) was added acetic anhydride (4.0 ml; 42.4 mmol). The mixture was heated to 80°C overnight. The solvent was removed under reduced pressure and the residue was washed several

times with a mixture of diethyl ether and petroleum ether (1:1 v/v) to leave **6q$_1$** as an oil (5.2 g; 72%).

2-(1-Acetyl-4-piperazinyl)-ethyl 3-nitrobenzoate (**6q**). To a solution of 3-nitrobenzoyl chloride (2.5 g; 13.5 mmol) in a mixture of THF (25 ml) and DMF (5 ml) was added triethylamine (1.87 ml; 13.5 mmol), a catalytic amount of 4-(N,N-dimethylamino)pyridine and **6q$_1$** (2.32 g; 13.5 mmol). The mixture was heated to 80°C for 2 hours whereafter the solvent was removed under reduced pressure. The residue was re-dissolved in dichloromethane and extracted with diluted hydrochloride acid (4 M). The aqueous phase was rendered alkaline by addition of aqueous sodium hydroxide (4 M) and extracted with dichloromethane. This extract was dried over sodium sulphate and concentrated under reduced pressure. The concentrate was purified by column-chromatography on silica gel using a mixture of dichloromethane, methanol and aqueous ammonia (90:10:1 v/v/v) as the eluent. Yield: 1.0 g (23%).

Example 6r



6r

(1-Methyl-2-pyrrolidyl)-methyl 3-nitrobenzoate (**6r**). To a solution of 3-nitrobenzoylchloride (2.5 g; 13.5 mmol) in THF (25 ml) was added triethylamine (1.87 ml; 13.5 mmol), a catalytic amount of 4-(N,N-dimethylamino)pyridine and (*S*)-(-)-1-methyl-2-pyrrolidinemethanol (1.61 ml; 13.5 mmol). The mixture was heated to reflux for 1.5 hours and left with stirring at ambient temperature overnight. The solvent was removed by evaporation and the residue was partitioned between dichloromethane and diluted hydrochloric acid (4 M). The aqueous phase was rendered alkaline by addition of aqueous sodium hydroxide (4 M) and extracted with dichloromethane. The organic extract was dried over sodium sulphate and evaporated to leave **6r** (2.8 g; 78%).

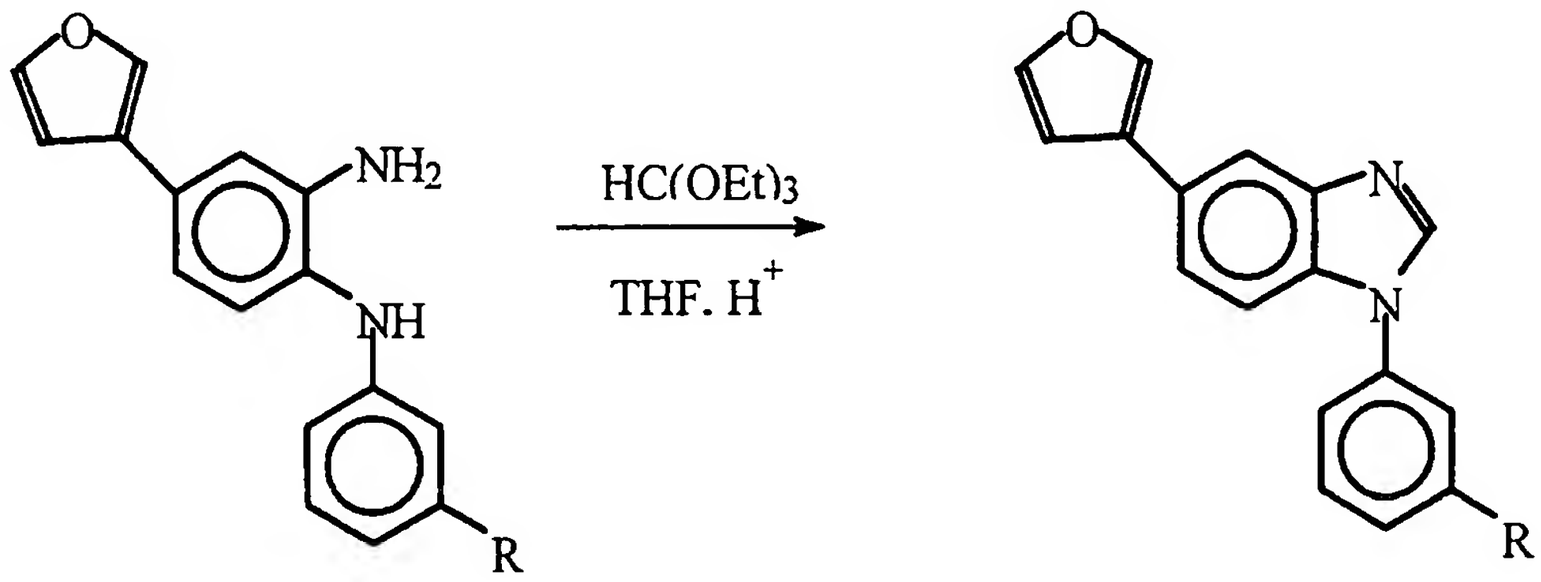
The concentrate was purified by column-chromatography on silica gel using a mixture of ethyl acetate and petroleum ether as the eluent (9:1 v/v). Yield: 2.6 g (38%).

Example 6u

1-(3-Nitrophenyl)-4-((1-methyl-5-tetrazolyl)-methyl)-piperazine (**6u**). A solution of **6t** (2.40 g; 10.0 mmol), sodium azide (1.43 g; 22.0 mmol) and ammonium chloride (0.64 g; 12.0 mmol) in DMF (25 ml) was heated to120°C over night. The cooled mixture was poured into ice-water and the precipitate was filtered off, washed with water and air-dried to leave a tetrazole (2.03 g).

This intermediary product was suspended in DMF (25 ml) in a nitrogen atmosphere and sodium hydride (0.28 g, 7.0 mmol) was added. When the evolution of hydrogen had ceased iodo-methane (0.44 ml; 7.1 mmol) was added and the mixture was stirred at ambient temperature for 4 hours. The mixture was diluted with four volumes of water and extracted with ethyl acetate. The extract was dried over magnesium sulphate and evaporated to dryness. The residue was trituated with a mixture of diethyl ether and petroleum ether (1:1 v/v) to leave **6u**. Yield: 0.95 g.

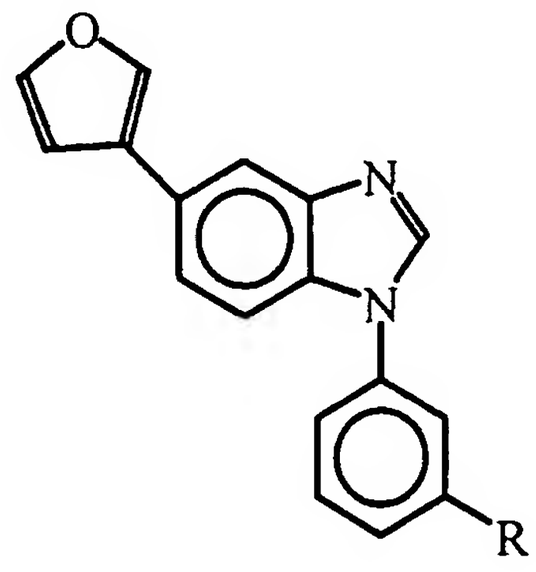
Example 7

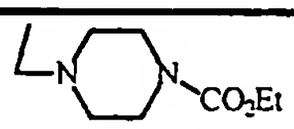
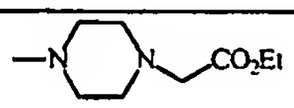
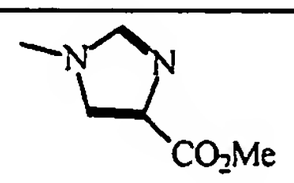
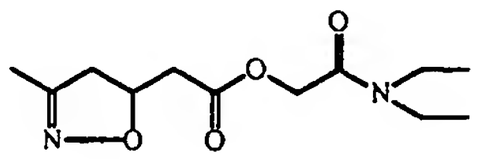
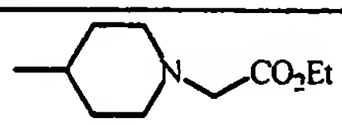
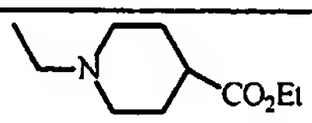
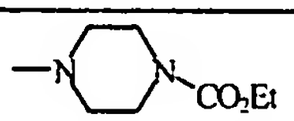
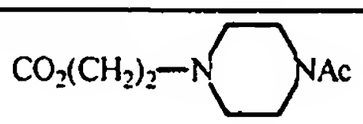
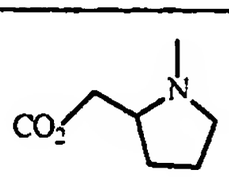


8 **7**

The furanyl substituted benzimidazoles of Table 5 were all prepared according to the above scheme as exemplified for compound **7a** below.

Table 5



Comp. No.	R	Mp (°C)	Yield (%)	Starting material	Salt
7a		248-250	100	**8a**	HCl
7b		113-114.5	83	**8b**	
7c		221-223	100	**8c**	
7d		131-132	37	**8d**	
7e		oil	77	**8e**	
7f		oil	47	**8f**	
7g		114-115	29	**8g**	
7h		oil	82	**8h**	
7i		131-132	48	**8i**	
7j		167-168	78	**8j**	HCl
7k		198-200	38	**8k**	HCl

5-(3-Furanyl)-1-(3-((4-ethoxycarbonyl-1-piperazinyl)-methyl)-phenyl)-benzimidazole (**7a**). To a solution of **8a** (0.13 g; 0.31 mmol) in THF was added triethyl orthoformiate (0.1 ml; 0.62 mmol) and a catalytic amount of p-toluenesulfonic acid. The mixture was heated to 80°C for 30 min. The cooled mixture was diluted with ethyl acetate and washed with aqueous sodium hydroxide and water, successively. The organic phase was dried over sodium sulphate and concentrated to a small volume. The product precipitated as the hydrochloride upon addition of ethereal hydrogen chloride. Filtration left the product, quantitatively. Mp. 248-250°C.

The following compound were prepared in analogy with Compound **7a**:

5-(3-Furanyl)-1-(3-(1-(ethoxy-carbonyl-methyl)-4-piperazinyl)-phenyl)-benzimidazole (**7b**) from **8b**. The product was purified on silica gel using a mixture of

ethyl acetate and ethanol (9:1 v/v) and was isolated as the free base. Mp. 113-114.5°C.

5-(3-Furanyl)-1-(3-(4-methoxycarbonyl-1-imidazolyl)-phenyl)-benzimidazole (**7c**) from **8c**. Mp. 221-223°C.

5-(3-Furanyl)-1-(3-(4-*t*-butoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole (**7d**) from **8d**. The product was purified on silica gel using ethyl acetate as the eluent and was isolated as the free base. Mp. 131-132°C.

N,N-Diethylcarbamoylmethyl 2-(3-(3-(5-(3-furanyl)-1-benzimidazolyl)-phenyl)-4,5-dihydroisoxazole-5-yl)-acetate (**7e**) from **8e**. The product was purified on silica gel using ethyl acetate as the eluent and was isolated as the free base.

5-(3-Furanyl)-1-(3-(1-ethoxycarbonylmethyl-4-piperazinylmethyl)-phenyl)-benzimidazole (**7f**) from **8f**. The product was purified on silica gel using a mixture of ethyl acetate and ethanol (9:1 v/v) as the eluent and was isolated as the free base.

5-(3-Furanyl)-1-(3-(1-ethoxycarbonylmethyl-4-piperidyl)-phenyl)-benzimidazole (**7g**) from **8g**. The product was purified on silica gel using ethyl acetate as the eluent and was isolated as the free base. Mp. 114.5-115°C.

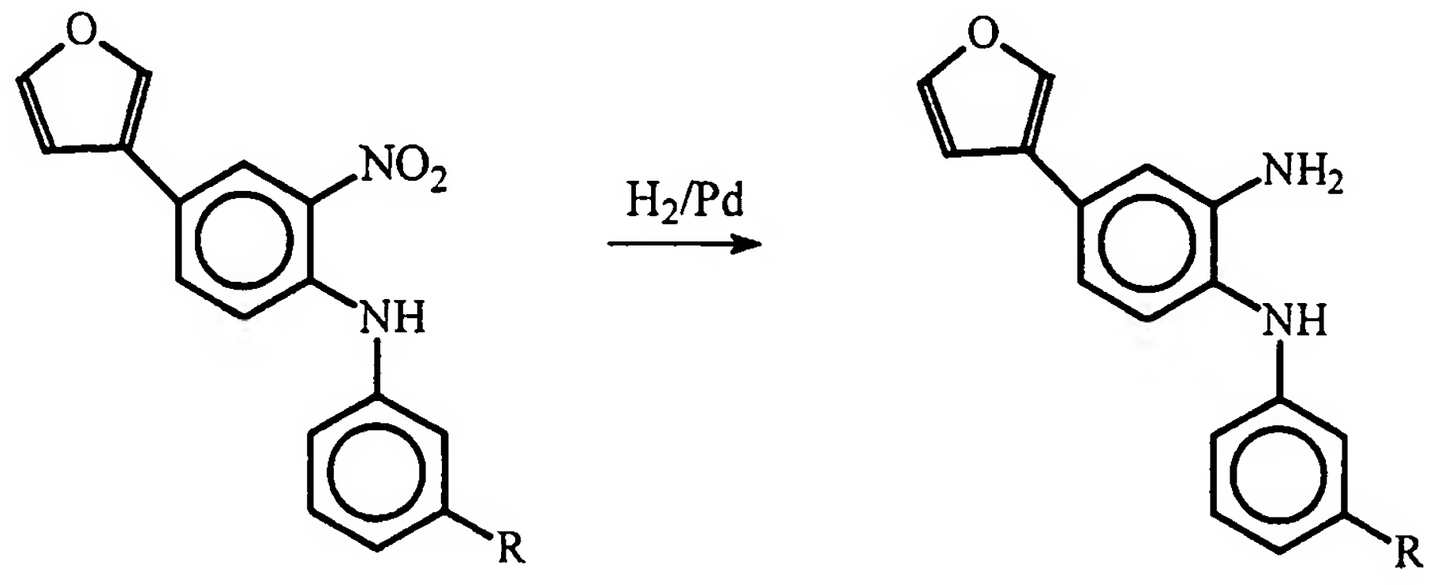
5-(3-Furanyl)-1-(3-(4-ethoxycarbonylpiperid-1-ylmethyl)-phenyl)-benzimidazole (**7h**) from **8h**. The product was purified on silica gel using a mixture of ethyl acetate and ethanol (9:1 v/v) as the eluent and was isolated as the free base.

5-(3-Furanyl)-1-(3-(1-ethoxycarbonyl-4-piperazinyl)-phenyl)-benzimidazole (**7i**) from **8i**. The product was purified on silica gel using ethyl acetate as the eluent and isolated as the free base. Mp. 131-132°C.

2-(1-Acetyl-4-piperazinyl)-ethyl 3-(5-(3-furanyl)-1-benzimidazolyl)-benzoate (**7j**) from **8j**. Mp. 167-168°C.

1-Methyl-2-pyrrolidylmethyl 3-(5-(3-furanyl)-1-benzimidazolyl)-benzoate (**7k**) from **8k**. Mp. 198-200°C.

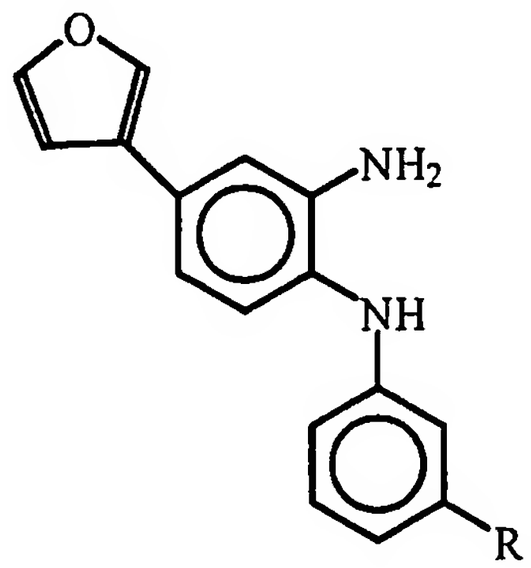
Example 8

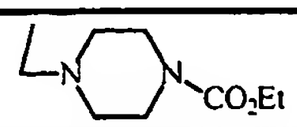
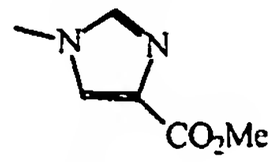
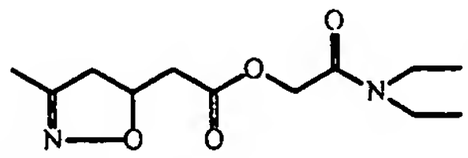
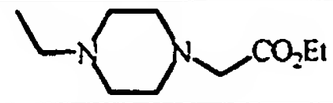
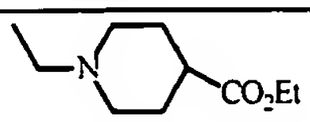
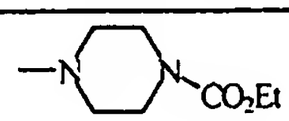
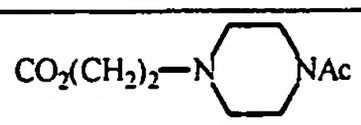
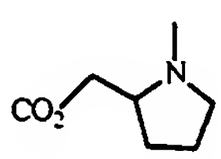


9 **8**

The furanyl substituted phenylenediamines of Table 6 were all prepared quantitatively by hydrogenation of the corresponding nitro compounds (**9**) as exemplified for compound **8a** below.

Table 6



Comp. No.	R	Starting material
8a		9a
8b		9b
8c		9c
8d		9d
8e		9e
8f		9f
8g		9g
8h		8h
8i		9i
8j		9j
8k		9k

2-Amino-4-(3-furanyl)-N-(3-(1-ethoxycarbonyl-4-piperazinylmethyl)-phenyl)-aniline (**8a**). To a suspension of **9a** (0.37 g; 0.82 mmol) in ethanol (10 ml) was added Pd-catalyst (5% Pd on activated carbon) and the mixture was hydrogenated until the hydrogen uptake had ceased. The mixture was filtered through celite and the solvent removed by evaporation to leave the desired product, quantitatively.

The following compound were prepared in analogy with Compound **8a**:

2-Amino-4-(3-furanyl)-N-(3-(1-ethoxycarbonylmethyl-4-piperazinyl)-phenyl)-aniline (**8b**) from **9b**.

2-Amino-4-(3-furanyl)-N-(3-(4-methoxycarbonyl-1-imidazolyl)-phenyl)-aniline (**8c**) from **9c** using methanol as the solvent.

2-Amino-4-(3-furanyl)-N-(3-(1-*t*-butoxycarbonyl-4-piperazinyl)-phenyl)-aniline (**8d**) from **9d** using THF as the solvent.

N,N-Diethylcarbamoylmethyl 2-(3-(3-(2-amino-4-(3-furanyl)-phenylamino)-phenyl)-4,5-dihydroisoxazolin-5-yl)-acetate (**8e**) from **9e** using THF as the solvent.

2-Amino-4-(3-furanyl)-N-(3-(1-ethoxycarbonylmethyl-4-piperazinylmethyl)-phenyl)-aniline (**8f**) from **9f**.

2-Amino-4-(3-furanyl)-N-(3-(1-ethoxycarbonyl-4-piperidyl)-phenyl)-aniline (**8g**) from **9g**.

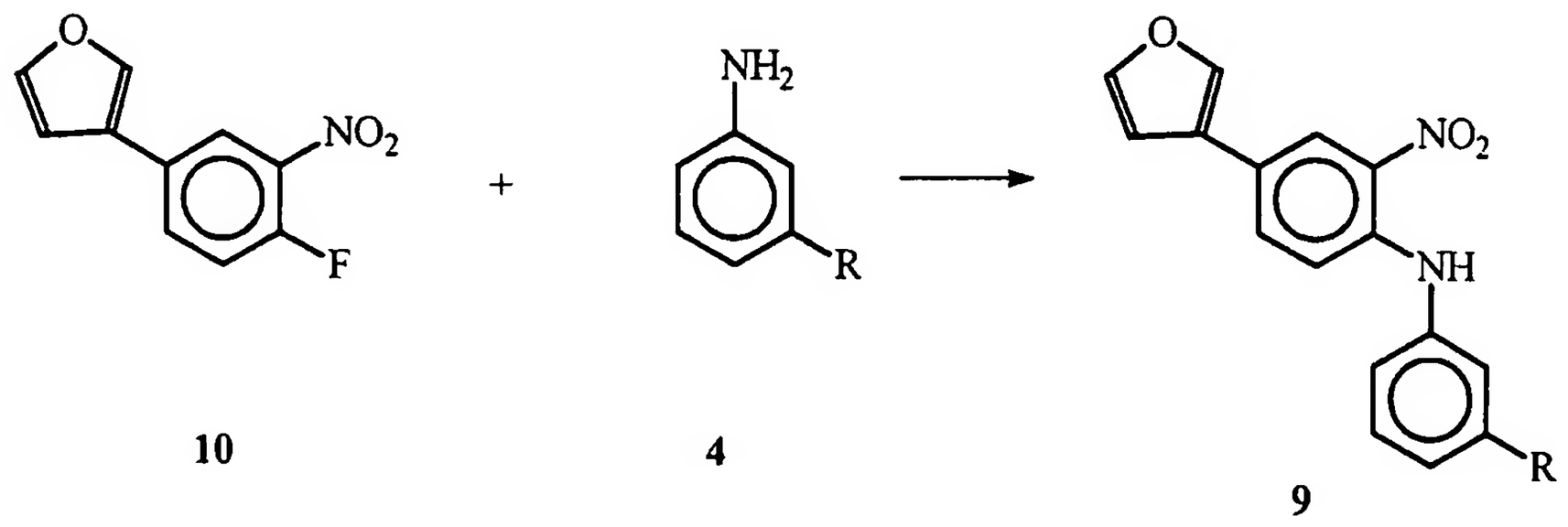
2-Amino-4-(3-furanyl)-N-(3-(4-ethoxycarbonyl-1-piperidylmethyl)-phenyl)-aniline (**8h**) from **9h**.

2-Amino-4-(3-furanyl)-N-(3-(4-ethoxycarbonyl-1-piperazinyl)-phenyl)-aniline (**8i**) from **9i**.

2-(4-Acetyl-1-piperazinyl)ethyl 3-(N-(2-amino-4-(3-furanyl)-phenyl)-amino)-benzoate (**8j**) from **9j** using THF as the solvent.

1-Methyl-2-pyrrolidylmethyl 3-(N-(2-amino-4-(3-furanyl)-phenyl)-amino)-benzoate (**8k**) from **9k** using THF as the solvent.

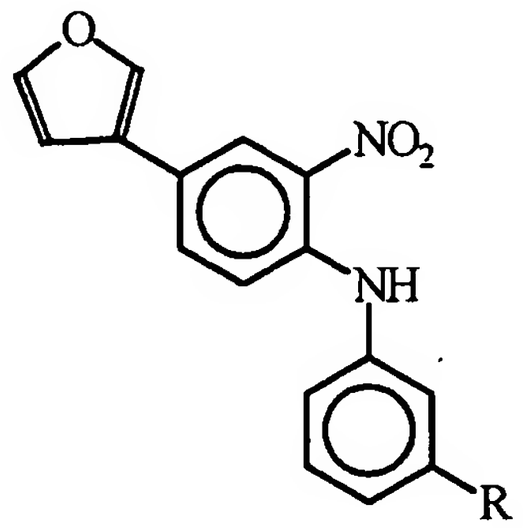
Example 9

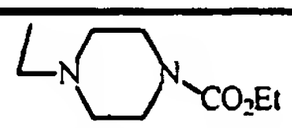
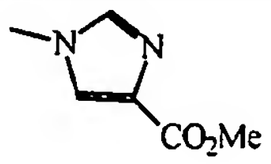
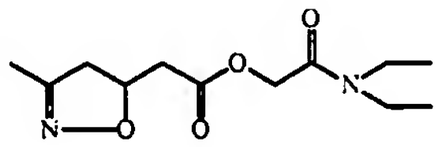
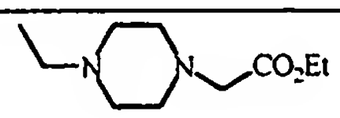
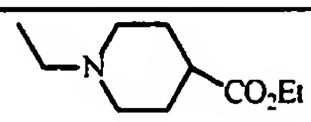
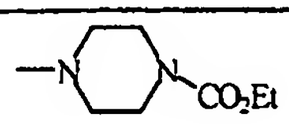
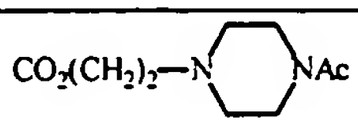
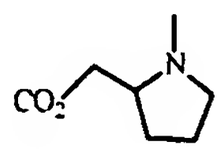


10 **4** **9**

The furanyl substituted nitroanilines of Table 7 were all prepared by reaction of **10** (prepared as described in WO 96/33194) with substituted anilines (**4** (see Example 4)) as described for compound **9a** below.

Table 7



Compound No.	R	Starting materials	Yield
9a		**10, 4a**	23
9b		**10, 4b**	10
9c		**10, 4c**	10
9d		**10, 4i**	61
9e		**10, 4k**	15
9f		**10, 4m**	13
9g		**10, 4n**	34
9h		**10, 4o**	38
9i		**10, 4p**	29
9j		**10, 4q**	51
9k		**10, 4r**	34

2-Nitro-4-(3-furanyl)-N-(3-(1-ethoxycarbonyl-4-piperazinylmethyl)-phenyl)-aniline (**9a**). To a solution of **10** (0.75 g; 3.61 mmol) in NMP (5 ml) was added triethylamine (0.53 ml; 3.61 mmol) and **4a** (1.0 g; 3.83 mmol). The mixture was heated to 110°C for two days and then poured into water and extracted with ethyl acetate. The organic extract was washed with brine, dried over magnesium sulphate and concentrated under reduced pressure. The concentrate was purified by column-chromatography on silica gel using a mixture of ethyl acetate and petroleum ether (1:1 v/v) as the eluent. Yield: 23%.

The following compound were prepared in analogy with Compound **9a**:

2-Nitro-4-(3-furanyl)-N-(3-(1-ethoxycarbonylmethyl-4-piperazinyl)-phenyl)-aniline (**9b**) from **10** and **4b**.

2-Nitro-4-(3-furanyl)-N-(3-(4-methoxycarbonyl-1-imidazolyl)-phenyl)-aniline (**9c**) from **10** and **4c**. Ethyl acetate was used as the eluent.

2-Nitro-4-(3-furanyl)-N-(3-(1-*t*-butoxycarbonyl-4-piperazinyl)-phenyl)-aniline (**9d**) from **10** and **4i**.

N,N-Diethylcarbamoylmethyl 2-(3-(3-(N-(2-nitro-4-(3-furanyl)-phenyl)-amino)-phenyl)-4,5-dihydroisoxazolin-5-yl)-acetate (**9e**) from **10** and **4k**. A mixture of ethyl acetate and petroleum ether (9:1 v/v) was used as the eluent.

2-Nitro-4-(3-furanyl)-N-(3-(1-ethoxycarbonylmethyl-4-piperazinylmethyl)-phenyl)-aniline (**9f**) from **10** and **4m**.

2-Nitro-4-(3-furanyl)-N-(3-(1-ethoxycarbonyl-4-piperidyl)-phenyl)-aniline (**9g**) from **10** and **4n**. Ethyl acetate was used as the eluent.

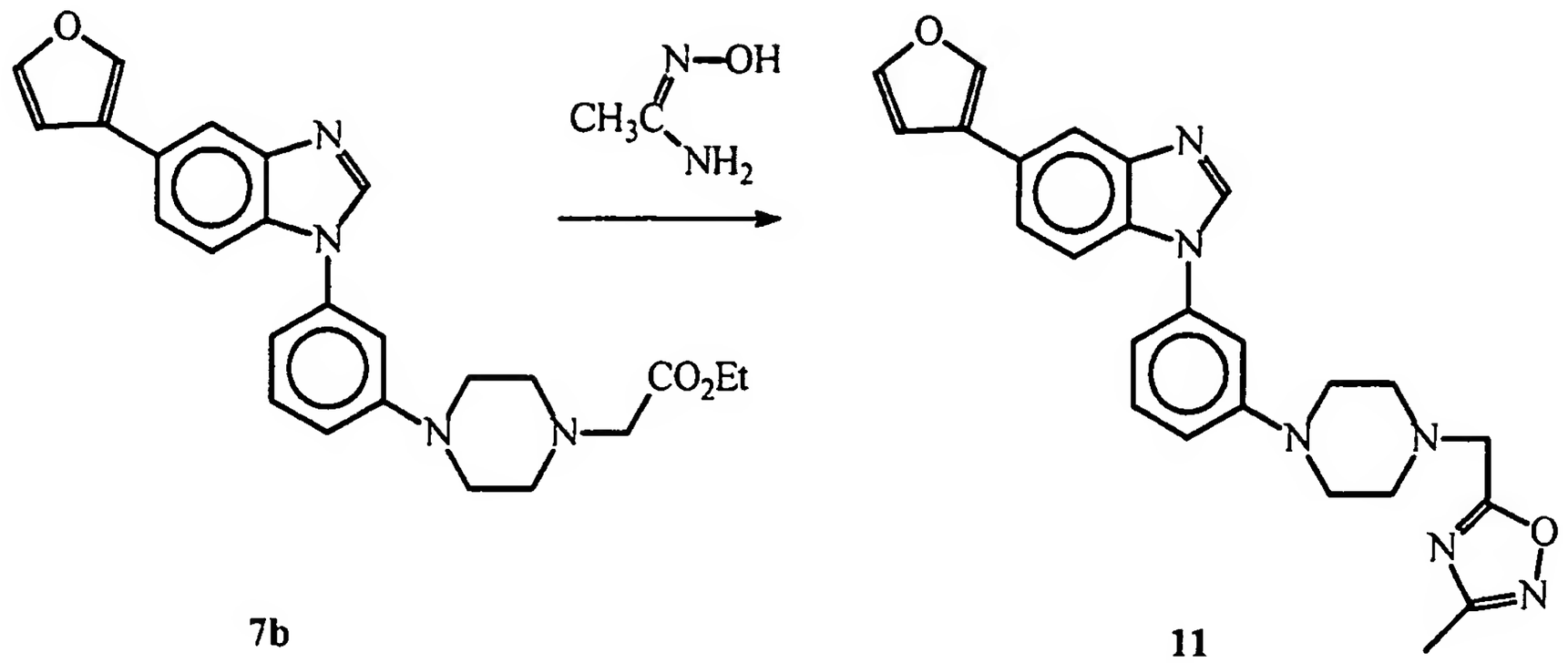
2-Nitro-4-(3-furanyl)-N-(3-(4-ethoxycarbonyl-1-piperidylmethyl)-phenyl)-aniline **9h** from **10** and **4o**.

2-Nitro-4-(3-furanyl)-N-(3-(4-ethoxycarbonyl-1-piperazinyl)-phenyl)-aniline (**9i**) from **10** and **4p**.

2-(4-Acetyl-1-piperazinyl)ethyl 3-(N-(2-nitro-4-(3-furanyl)-phenyl)-amino)-benzoate (**9j**) from **10** and **4q**. Ethyl acetate was used as the eluent.

1-Methyl-2-pyrrolidylmethyl 3-(N-(2-nitro-4-(3-furanyl)-phenyl)-amino)-benzoate (**9k**) from **10** and **4r**. A mixture of dichloromethane, methanol and aqueous ammonia (90:10;1) was used as the eluent.

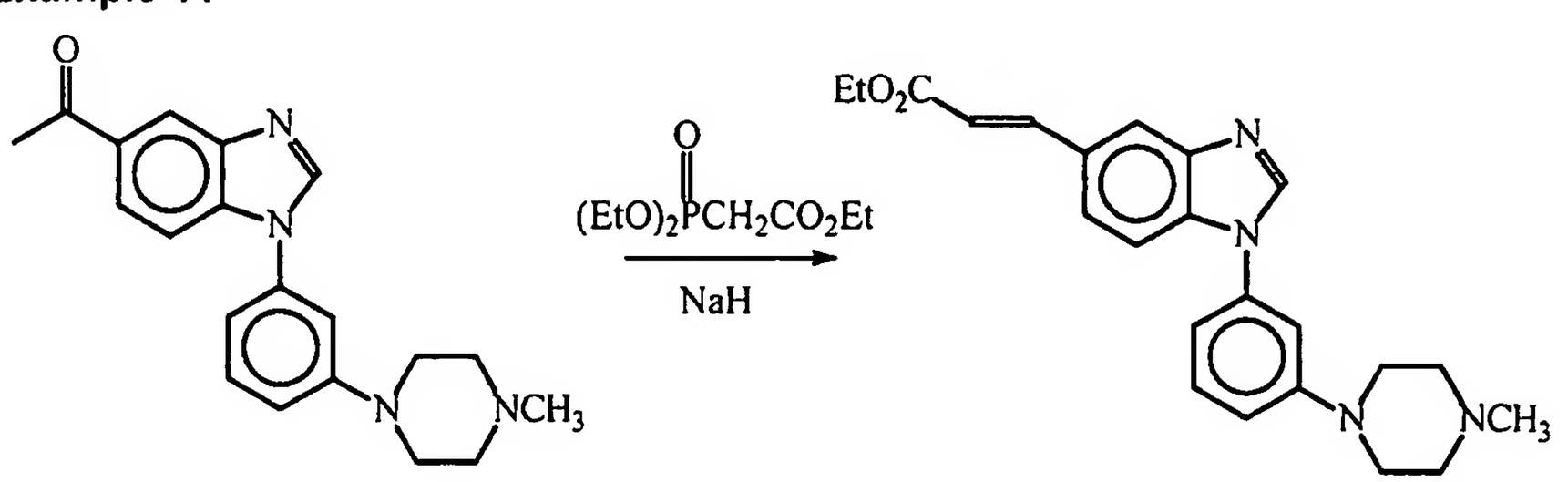
Example 10



7b **11**

5-(3-Furanyl)-1-(3-(1-(3-methyl-5-oxadiazolylmethyl)-4-piperazine)-phenyl)-benzimidazole (**11**). To a solution of sodium (0.12 g; 5.2 mmol) in abs. ethanol (10 ml) was added molecular sieves (0.5 g), acetamide-oxime (0.19 g; 2.57 mmol) and **7b** (1.0 g; 2.32 mmol). The mixture was heated to reflux overnight. The cooled suspension was diluted with dichloromethane (50 ml) and stirred until all organic material had dissolved. The molecular sieves were filtered off and the filtrate was washed with water and brine, dried over sodium sulphate and evaporated to dryness. The residue was dissolved in toluene and a catalytic amount of p-toluenesulfonic acid was added. The mixture was heated to 100°C overnight, whereafter the cooled mixture was washed with aqueous sodium carbonate, dried over sodium sulphate and evaporated to dryness. The residue was triturated with diethyl ether to yield **11** (0.47 g; 46%). Mp. 129-130°C.

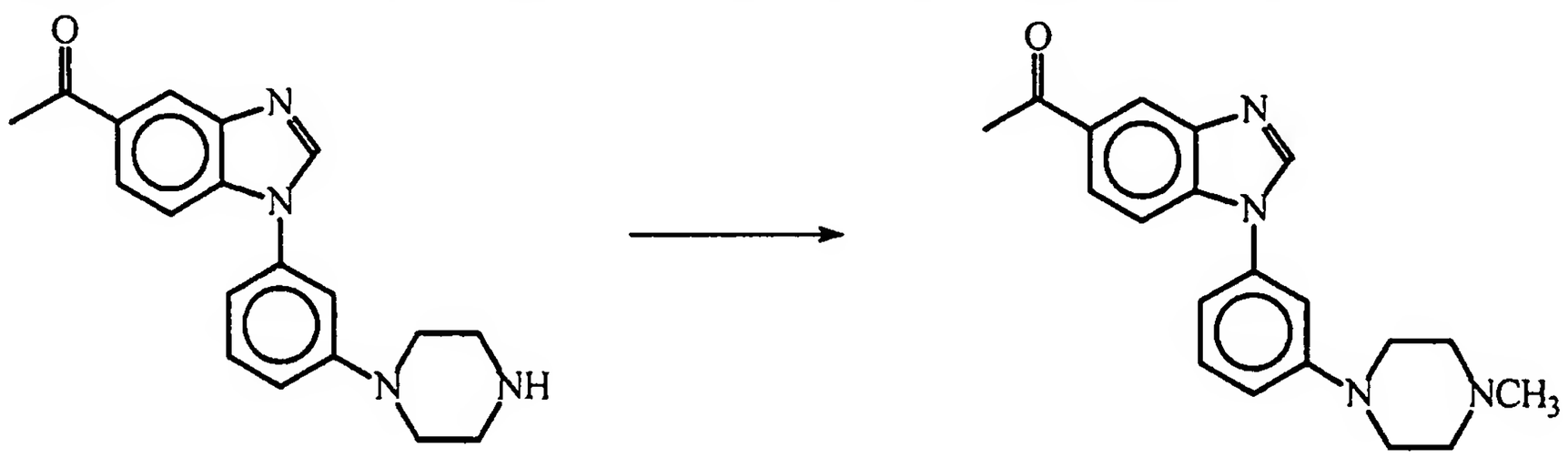
Example 11



13 **12**

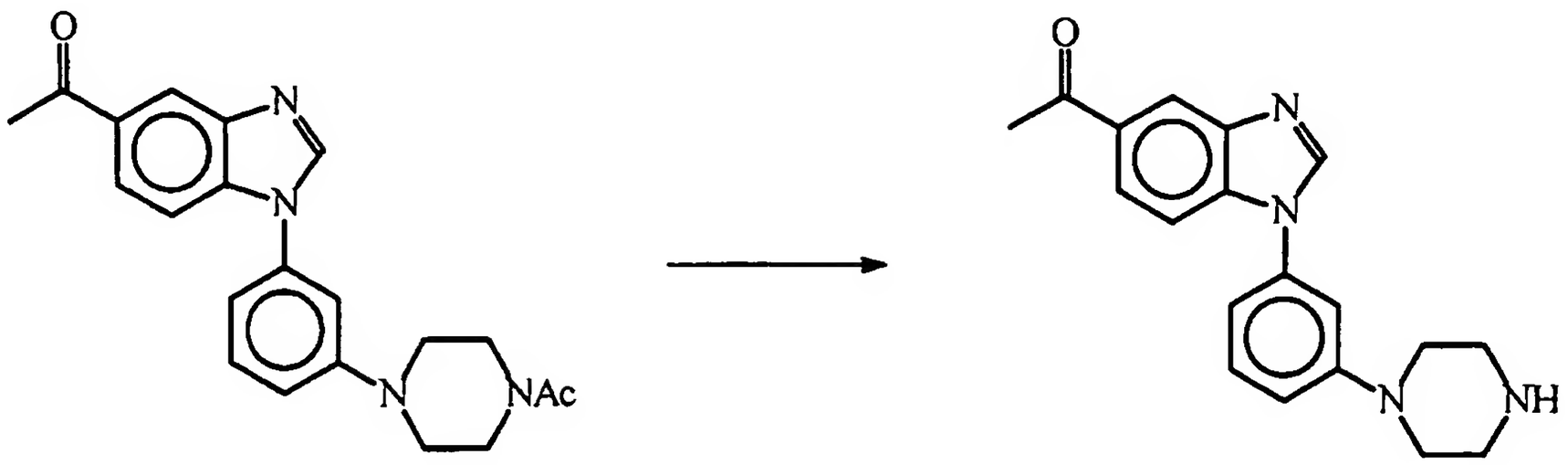
Ethyl (E)-3-(1-(3-(4-methyl-1-piperazinyl)-phenyl)-benzimidazol-5-yl)-propenoate (**12**). To a suspension of sodium hydride (40 mg, 60% dispersion in mineral oil, 1.0 mmol) kept in an inert atmosphere was added triethylphosphone-

acetate (0.2 ml; 1.0 mmol). The mixture was stirred at ambient temperature until a clear solution had formed. A solution **13** (0.33 g; 0.94 mmol) in anhydrous toluene (5 ml) was added. Stirring was continued for 15 min at room temperature whereafter the temperature was raised to 60-65°C overnight. The solvents were removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The phases were separated and the aqueous phase was extracted thrice with ethyl acetate. The combined organic extracts were dried over magnesium sulphate and concentrated. The concentrate was purified by column-chromatography on silica gel using a mixture of dichloromethane, methanol and aqueous ammonia (90:10:1 v/v/v) as the eluent. The product-containing fractions were evaporated to dryness, re-dissolved in abs. ethanol and precipitated as the hydrochloride by addition of ethereal hydrogen chloride. Yield: 0.28 g (68%). Mp. 180-190°C (with decomposition).



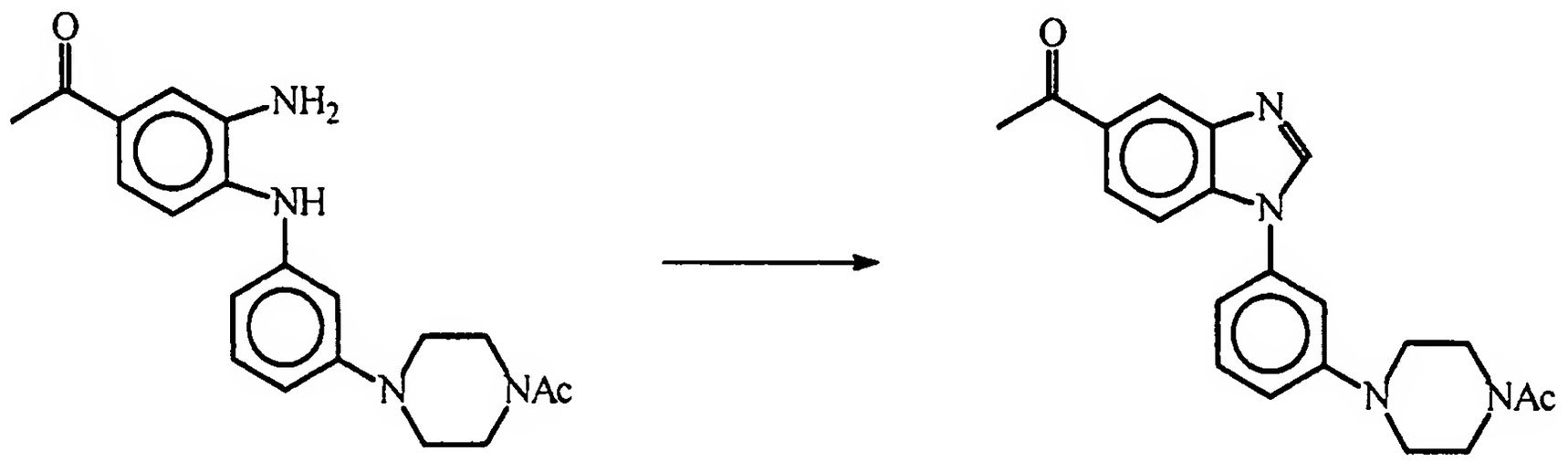
14 **13**

5-Acetyl-1-(3-(4-methyl-1-piperazinyl)-phenyl)-benzimidazole (**13**). To a solution of **14** (0.75 g; 2.34 mmol) in anhydrous DMF (10 ml) was added sodium hydride (0.1 g, 60% dispersion in mineral oil). The mixture was stirred for 30 min and iodo-methane (0.15 ml; 2.34 mmol) was added. After one hour the mixture was poured into ice-water and extracted with ethyl acetate. The extract was dried over magnesium sulphate and concentrated under reduced pressure. The concentrate was purified by column-chromatography using mixtures of ethyl acetate and methanol (9:1 v/v, 1:1 v/v), successively as eluents. Yield: 0.34 g (41%).



15 14

5-Acetyl-1-(3-(1-piperazinyl)-phenyl)-benzimidazole (**14**). To a solution of **15** (8.3 g; 23.0 mmol) in dimethoxyethane (140 ml) was added aqueous sodium hydroxide (70 ml; 1 M) and the mixture was heated to reflux overnight. The volatile solvent was removed and the aqueous suspension was extracted with dichloromethane. This extract was dried over sodium sulphate, concentrated and eluted through a silica gel column with a mixture of dichloromethane, methanol and aqueous ammonia (90:10:1 v/v/v). Yield: 4.8 g (65%).

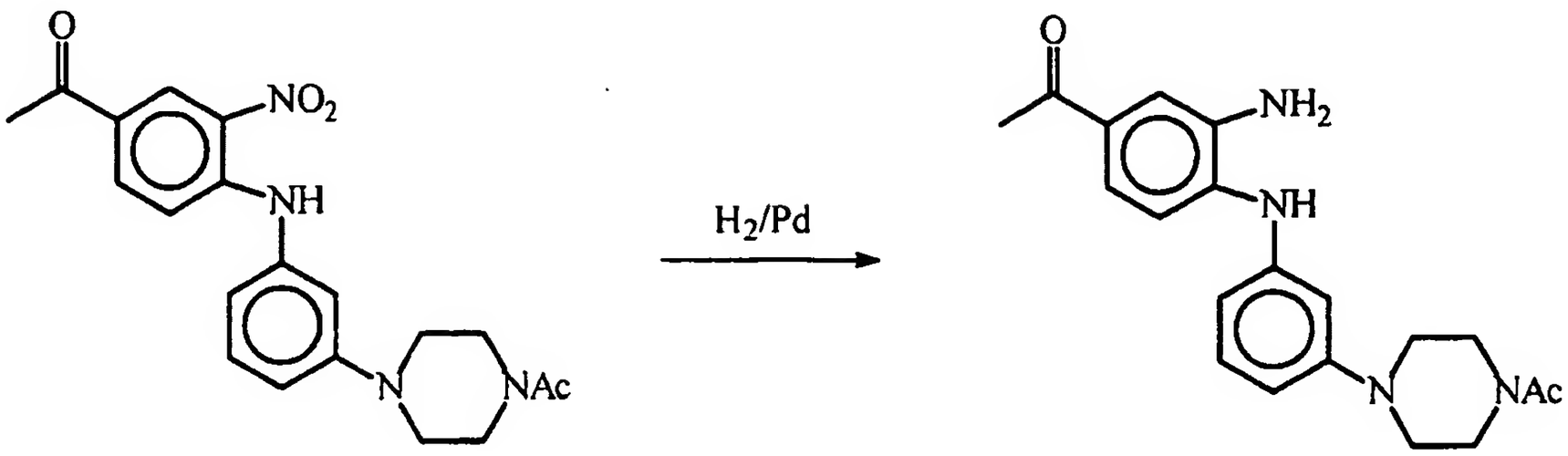


16 15

5-Acetyl-1-(3-(1-acetyl-4-piperazinyl)-phenyl)-benzimidazole (**15**). **16** (17.7 g; 50.3 mmol) was treated with triethyl orthoformiate as described in Example 1. The product was purified by column-chromatography on silica gel using a mixture of dichloromethane, methanol and aqueous ammonia (90:10:1 v/v/v) as the eluent. Yield: 16.0 g (88%).

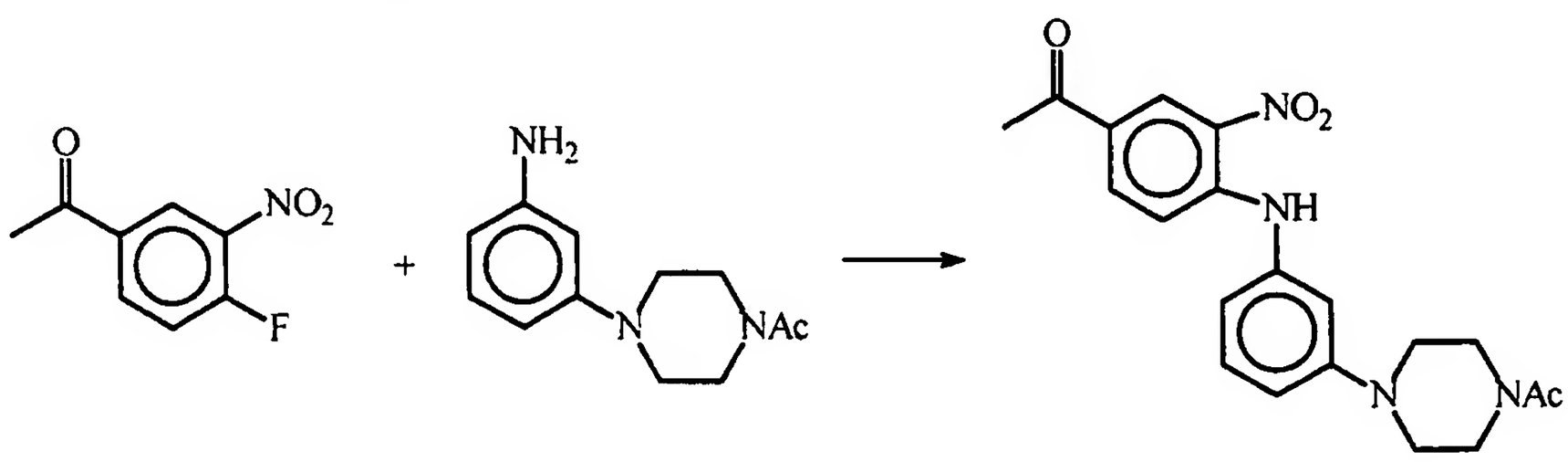
2-(3,5-dimethyl-1-piperazinyl)ethyl 3-(5-acetylbenzimidazol-1-yl)-benzoate was prepared analogously to **15**. The compound was treated hydroxylamine hydrochloride in abs. ethanol to yield 2-(3,5-dimethyl-1-piperazinyl)ethyl 3-(5-acetylbenzimidazol-1-yl)-benzoate oxime (**15a**) Mp. 255-260°C.

2-(2-pyridyl)methyl 3-(5-acetylbenzimidazol-1-yl)-benzoate was prepared analogously to **15**. This compound was treated hydroxylamine hydrochloride in abs. ethanol to yield 2-(2-pyridyl)-methyl 3-(5-acetylbenzimidazol-1-yl)-benzoate oxime (**15b**) Mp. 162-163°C.



17 16

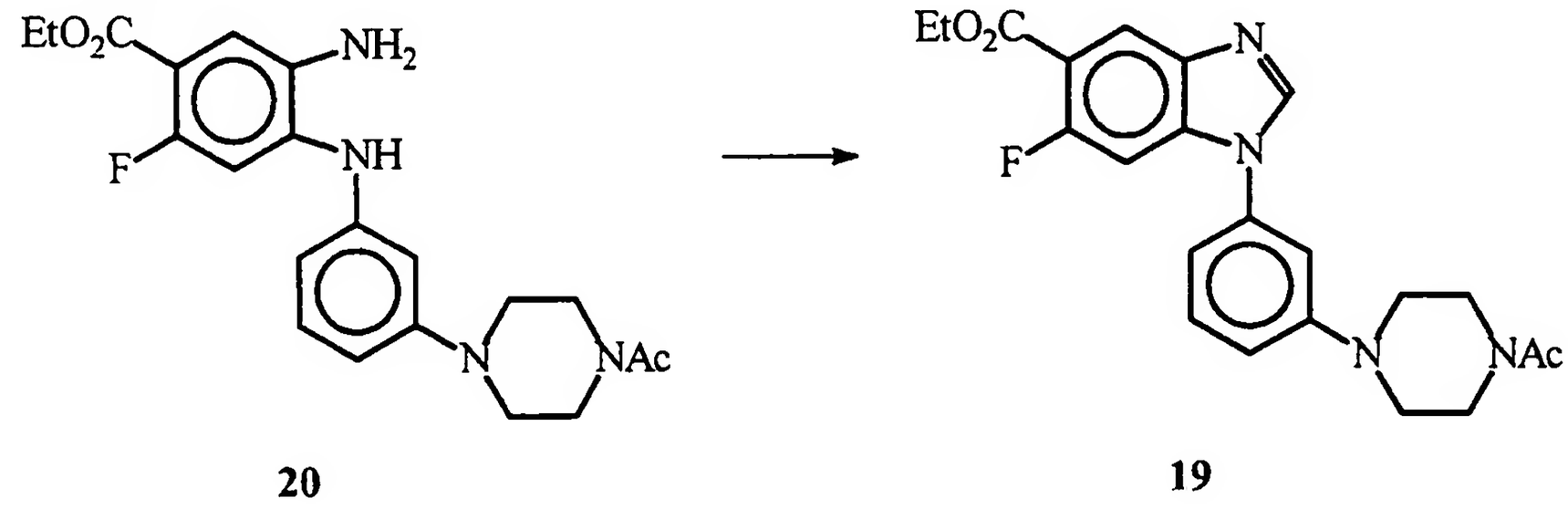
N-(4-Acetyl-2-aminophenyl)-3-(1-acetyl-4-piperazinyl)-aniline (**16**). **17** (45 g; 93.6 mmol) was hydrogenated as described in Example 2 to yield **16**, quantitatively.



18 4f 17

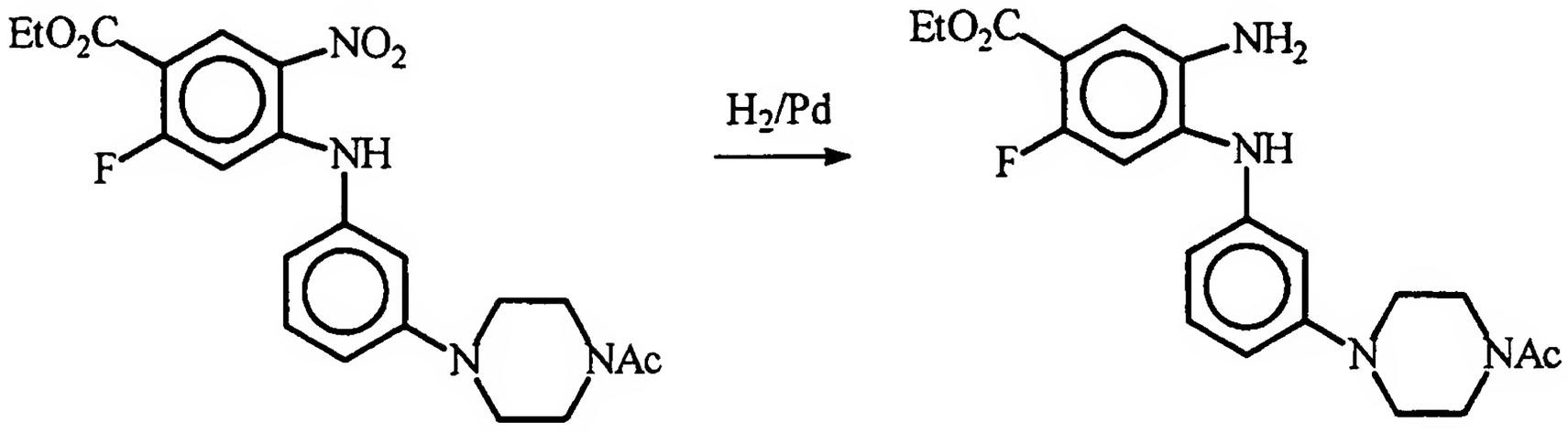
N-(4-Acetyl-2-nitrophenyl)-3-(1-acetyl-4-piperazinyl)-aniline (**17**). To a solution of **18** (17.1 g; 93.6 mmol) (prepared as previously described: WO 96/33191) and triethylamine (13 ml; 93.6 mmol) in anhydrous NMP (50 ml) was added **4f** and the mixture was heated to 80°C for four hours. The cooled mixture was poured into ice-water and extracted thrice with ethyl acetate. The organic extract was dried over sodium sulphate and evaporated to dryness to leave **17**, quantitatively.

Example 12



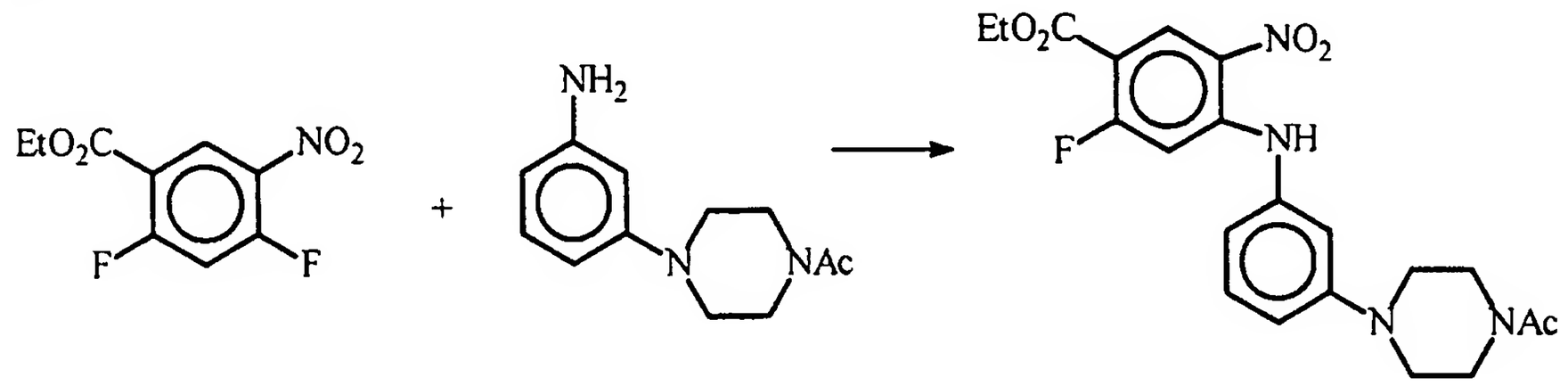
20 19

Ethyl 1-(3-(4-acetyl-1-piperazinyl)-phenyl)-6-fluorobenzimidazole-5-carboxylate (**19**) was prepared analogously to Example 1 from **20**. A mixture of ethyl acetate and ethanol (9:1 v/v) was used as the eluent. Yield: 55%. Mp. undefined.



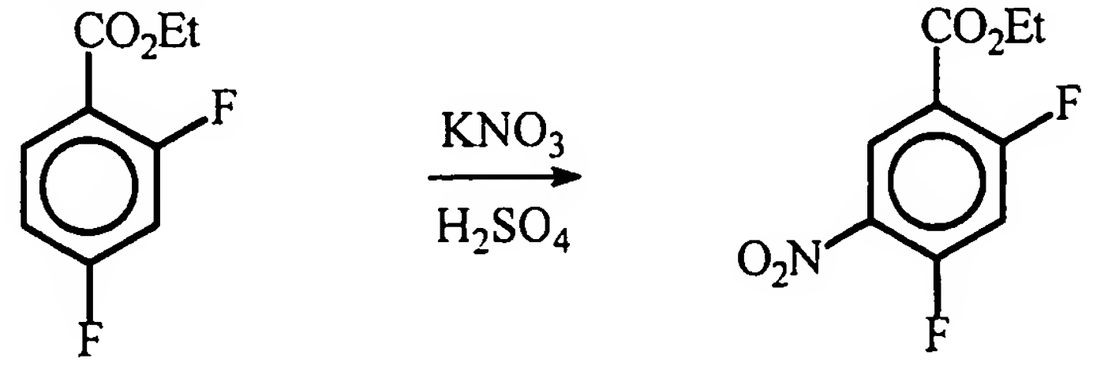
21 20

Ethyl 3-amino-4-(3-(4-acetyl-1-piperazinyl)-phenyl)-amino-6-fluorobenzoate (**20**) was prepared from **21** in analogy with Example 2. Abs. ethanol was used as solvent. Quantitative yield.



22 4f 21

Ethyl 4-(3-(4-acetyl-1-piperazinyl)-phenyl)-amino-6-fluoro-3-nitrobenzoate (**21**). A mixture of ethyl 2,4-difluoro-5-nitrobenzoate (**22**) (1.0 g; 4.33 mmol), **4f** (0.95 g; 4.33 mmol) and triethylamine (0.6 ml; 0.33 mmol) in anhydrous NMP (10 ml) was heated to 80°C for one hour. The cooled mixture was poured into water and extracted with ethyl acetate. The organic extract was dried over magnesium sulphate, concentrated under reduced pressure and purified by column-chromatography on silica gel using ethyl acetate as the eluent. Yield: 1.53 g (82%).



22

Ethyl 2,4-difluoro-5-nitrobenzoate (**22**). To a cooled (-5-0°C) solution of ethyl 2,4-difluorobenzoate (3.4 g; 18.3 mmol) in conc. sulphuric acid (6 ml) was added potassium nitrate (1.94 g; 19.2 mmol) in small portions over one hour -5°C. Following the addition the temperature was allowed to raise to 20°C over 4.5 hours. The mixture

was poured into ice-water with vigorous stirring. The product was filtered off, washed with water and air-dried. Yield: 3.2 g (76%).

Example 13

***In vitro* and *in vivo* Binding Activity**

The GABA recognition site and the benzodiazepine modulatory unit can selectively be labelled with ^{3}H-muscimol and ^{3}H-flunitrazepam, respectively.

13A: *In vitro* inhibition of ^{3}H-flunitrazepam (^{3}H-FNM) binding

Tissue Preparation

Preparations are performed at 0-4°C unless otherwise indicated. Cerebral cortex from male Wistar rats (150-200 g) is homogenised for 5-10 sec in 20 ml Tris-HCl (30 mM, pH 7.4) using an Ultra-Turrax homogeniser. The suspension is centrifuged at 27,000 x g for 15 min and the pellet is washed three times with buffer (centrifuged at 27,000 x g for 10 min). The washed pellet is homogenized in 20 ml of buffer and incubated on a water bath (37°C) for 30 min to remove endogenous GABA and then centrifuged for 10 min at 27,000 x g. The pellet is then homogenized in buffer and centrifuged for 10 min at 27,000 x g. The final pellet is resuspended in 30 ml buffer and the preparation is frozen and stored at -20°C.

Assay

The membrane preparation is thawed and centrifuged at 2°C for 10 min at 27,000 x g. The pellet is washed twice with 20 ml 50 mM Tris-citrate, pH 7.1 using an Ultra-Turrax homogeniser and centrifuged for 10 min at 27,000 x g. The final pellet is resuspended in 50 mM Tris-citrate, pH 7.1 (500 ml buffer per g of original tissue), and then used for binding assays. Aliquots of 0.5 ml tissue are added to 25 µl of test solution and 25 µl of ^{3}H-FNM (1 nM, final concentration), mixed and incubated for 40 min at 2°C. Non-specific binding is determined using Clonazepam (1 µM, final concentration). After incubation the samples are added 5 ml of ice-cold buffer and poured directly onto Whatman GF/C glass fibre filters under suction and immediately washed with 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

Results

25-75% inhibition of specific binding must be obtained, before calculation of an IC_{50}.

The test value will be given as IC_{50} (the concentration (μM) of the test substance which inhibits the specific binding of ^{3}H-FNM by 50%).

$$IC_{50} = (\text{applied test substance concentration, } \mu M) \times \frac{1}{\left(\frac{C_o}{C_x} - 1\right)}$$

where

C_o is specific binding in control assays, and

C_x is the specific binding in the test assay.

(The calculations assume normal mass-action kinetics).

The results from these experiments are shown in Table 8 below.

13B: *In vivo* inhibition of ^{3}H-FNM binding

Introduction

In vitro binding studies have demonstrated that the benzodiazepine [^{3}H]FNM binds selectively and with high-affinity to the $GABA_A$ receptor-ion channel complex. [^{3}H]FNM can also be used for *in vivo* receptor labelling studies in mouse. Accumulation of [^{3}H]FNM binding will occur all over the brain as $GABA_A$ receptors are widely distributed. The specific binding of [^{3}H]FNM can be partly or completely prevented by simultaneous or prior administration of pharmacologically active benzodiazepines or by some benzodiazepine-like compounds.

Method

All test substances used are solutions prepared in 10% TWEEN 80. Groups of three female NMRI mice (25 g) are injected i.v. via the tail vein with 5.0 μCi of [^{3}H]FNM in 0.2 ml saline. Fifteen min after injection with [^{3}H]FNM the test substance is administered i.v. Twenty min after injection with [^{3}H]FNM, mice are killed by decapitation, the forebrains rapidly excised and homogenized in 12 ml of ice-cold 50 mM Tris-citrate, pH 7.1 using an Ultra-Turrax homogenizer. Three aliquots of 1 ml are immediately filtered through GF/C glass fibre filters and washed with 2 × 5 ml of ice-cold buffer. The amounts of radioactivity on the filters and in 200 μl of the homogenate are determined by conventional scintillation counting. Groups of untreated mice serves as controls. To determine non-specific binding groups of mice are injected with Clonazepam (25 mg/kg) i.p. 10 min before [^{3}H]FNM injection. Specific binding is the amount of binding in controls minus the amount of binding in Clonazepam treated mice.

Results

The ED_{50} value is determined from dose response curves. If only one dose of test substance is administered, the ED_{50} value is calculated as follows, provided that the inhibition of specific binding is within the range of 25-75%.

$$ED_{50} = (\text{administered dose, mg/kg}) \times \frac{1}{\left(\frac{C_o}{C_x} - 1\right)}$$

where C_o is specific binding in controls and C_x is the specific binding in mice treated with test substance.

The results from these experiments are shown in Table 8 below.

Table 8

Test compound	***In vitro* binding IC_{50} (µM)**	***In vivo* binding ED_{50} (mg/kg)**
Of the invention:		
1b	0.26	0.9
7j	0.0028	1.9
7i	0.0008	1.8
7g	0.0009	1.4
7c	0.0007	0.43
1l	0.012	0.75
7f	0.0006	0.17
Reference compounds:		
Compound $4d_3$ of WO 98/17651	0.06	0.22
Compound 4j of WO 98/17651	1.1	13.3
Compound 4m of WO 98/17651	1.0	6

Example 14

PTZ Clonic Convulsions

The purpose of this test is to show antagonism of clonic convulsions induced by pentylenetetrazol (PTZ). PTZ induces clonic convulsions in mice after i.v. infusion. Antagonism of PTZ-induced convulsions is a measure for the agonistic character of ligands for the benzodiazepine recognition site.

Procedure

Female NMRI mice (Bomholdtgaard, Ry), 20 g, 6 mice in each group are administered i.v. with vehicle or test substance. After five minutes the PTZ-solution is infused intravenously at a speed of 0.7 ml/minute through a cannula placed in the tail vein. The time from initiation of the infusion to appearance of clonic convulsions is recorded.

The dose of PTZ required for inducing convulsion in each mouse is calculated as PTZ/kg body weight. Means ±sd for each experimental group of 6 mice is calculated. ED_{100} is calculated by linear regression expressing the dose increasing the PTZ threshold to 100 mg PTZ/kg.

The threshold of vehicle treated controls is in the range of 37-39 mg PTZ/kg. As a control in each series of experiments PTZ is infused into 6 vehicle treated mice.

The results from these experiments are shown in Table 9 below.

Table 9

Test compound	ED_{100} (mg/kg)	ptz threshold at 30mg/kg (mg/kg)
Of the invention:		
1b	1.6	200
7j	13	170
7i	2.5	140
7g	1.2	200
7c	20	110
1l	17	120
7f	2.7	120
Reference compounds:		
Compound $4d_3$ of WO 98/17651	0.16	230

Test compound	ED_{100} (mg/kg)	ptz threshold at 30mg/kg (mg/kg)
Compound 4j of WO 98/17651	16	140
Compound 4m of WO 98/17651	9	175

Example 15

Evaluation of Efficacy

Selected compounds exhibiting a promising profile in the above tests were evaluated with respect to efficacy and duration of action and compared to prior art as follows.

Aqueous solutions of the test substances (50 mg/ml isotonic glucose) were administered to pigs (25-30 kg) as bolus injections. The actual dose of each substance is included in the table below. The pigs were observed with respect to the time of induction of anaesthesia, the duration of anaesthesia and the normalising time following awakening from anaesthesia.

These observations are compiled in Table 10 below. This table also provides comparative data for compounds of the prior art (WO 98/17651).

Table 10

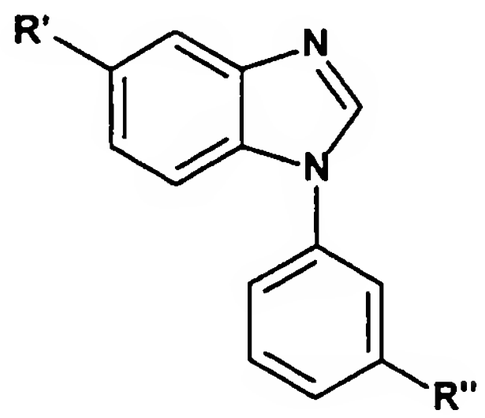
Compound No.	Bolus dose (mg/kg)	Induction Time (min.)	Maintained anaesthesia (min.)	Normalising time following awakening (min.)
7j	3	0,5	8[a]	20
1b	0,6	1,3	10	15
Compound $4d_3$ of WO 98/17651	0,03	0,75	60	120
Compound 4j of WO 98/17651	3	1,0	0[b]	-
Compound 4m of WO 98/17651	3	-	0[c]	-

[a] Uneasy sleep
[b] light sleep/sedation
[c] only mild sedation observed

From the table it can be concluded, that the compounds of the present invention has a very advantageous profile regarding the induction time, duration of action and recovery time. Compared to the compounds of prior art, which shows either a too weak anaesthesising effect or a too long recovery time, the compounds provided by the present invention meet the criteria for promising anaesthetics.

Claims:

1. A benzimidazole derivative represented by the general Formula I,



(I)

or a pharmaceutically acceptable salt thereof,

wherein,

R' represents a group of the formula $-(alk)_q-R^1$,

wherein

(alk) represents alkyl, alkenyl or alkynyl,

q is 0 or 1,

R^1 represents a group of the formula $-CO_2R^2$, wherein

R^2 represents hydrogen, alkyl, hydroxy-alkyl, alkoxy-alkyl, thioalkoxy-alkyl, alkyl-"Heterocycle", or $-alkyl-NR^3R^4$,

wherein

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, and a group of the formula $-(alkyl)_p-CN$, $-(alkyl)_p-aryl$, $-(alkyl)_p-$"Heterocycle", $-(alkyl)_p-CO_2-$"Heterocycle" or $-(alkyl-CO_2)_s-(alkyl)_t-COR^5$,

in which formulas

p, s and t independently of each another is 0 or 1,

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl,

R^5 represents hydroxy, alkoxy, hydroxy-alkoxy, alkoxy-alkoxy, thioalkoxy-alkoxy, or a group of the formula $-NR^6R^7$ or $-O-alkyl-NR^6R^7$,

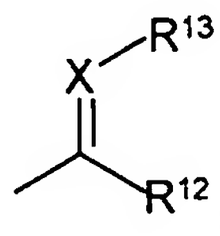
in which formulas

R^6 and R^7 independently of each another represent hydrogen, alkyl, cycloalkyl or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, or

R^6 and R^7 together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group may be substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl; and

R^3 and R^4 independently of each another represent hydrogen, alkyl or cycloalkyl, or

R^3 and R^4 together with the nitrogen to which they are attached form a mono- or poly-cyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl; or

R^1 represents a group of the formula  , wherein

X represents N or CH,

R^{12} represents hydrogen, alkyl, alkoxy or hydroxy-alkyl, and

R^{13} represents hydrogen, hydroxy, alkyl, alkoxy or hydroxy-alkyl; or

R^1 represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, hydroxy-alkyl, alkoxy-alkyl, carboxyl, and acyl, and a group of the formula $-(alkyl)_p$-aryl, $-(alkyl)_p$-"Heterocycle", $-(alkyl)_p$-CN or $-(alkyl\text{-}CO_2)_s$-$(alkyl)_t$-COR^5,

in which formulas

p, s and t independently of each another is 0 or 1,

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl,

R^5 represents hydroxy, alkoxy, hydroxy-alkoxy, alkoxy-alkoxy, thioalkoxy-alkoxy, or a group of the formula $-NR^6R^7$ or -O-alkyl-NR^6R^7,

in which formulas

R^6 and R^7 independently of each another represent hydrogen, alkyl, cycloalkyl or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, or

R^6 and R^7 together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl; and

R'' represents $-(alkyl)_o$-"Heterocycle" or $-(alkyl)_o-CO_2-(alkyl)_u$-"Heterocycle",

wherein

o and u independently of each another is 0 or 1, and

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl, and acyl, and a group of the formula $-(alkyl)_p$-CN, $-(alkyl)_p$-aryl, $-(alkyl)_p$-aralkyl, $-(alkyl)_p$-O-aryl, $-(alkyl)_p$-O-aralkyl, $-(alkyl)_p-CO_2$-aryl, $-(alkyl)_p-CO_2$-aralkyl, $-(alkyl)_p$-"Heterocycle", $-(alkyl)_p-CO_2$-"Heterocycle" or $-(alkyl-CO_2)_s-(alkyl)_t-COR^5$,

in which formulas

p, s and t independently of each another is 0 or 1,

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl,

R^5 represents hydrogen, hydroxy, alkyl, alkoxy, hydroxy-alkyl, hydroxy-alkoxy, alkoxy-alkyl, alkoxy-alkoxy, thioalkoxy-alkyl, thioalkoxy-alkoxy, or a group of the formula $-NR^6R^7$ or -O-alkyl-NR^6R^7,

in which formulas

R^6 and R^7 independently of each another represent hydrogen, alkyl, cycloalkyl or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of

halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, or

R^6 and R^7 together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl; or

R'' represents $-(alkyl)_m-CO_2R^8$,

wherein

m is 0 or 1, and

R^8 represents hydrogen, alkyl, hydroxy-alkyl, alkoxy-alkyl, thioalkoxy-alkyl, or a group of the formula $-(alkyl)_p-NR^9R^{10}$,

wherein

p is 0 or 1, and

R^9 and R^{10} independently of each another represent hydrogen, alkyl, cycloalkyl, or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl, or

R^9 and R^{10} together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl.

2. The benzimidazole derivative of claim 1, wherein R'' represents

2-(4-acetylpiperazin-1-yl)-ethoxy-carbonyl;

pyridin-2-yl-methoxy-carbonyl;

1-Methyl-2-pyrrolidyl-methoxy-carbonyl; or

3,5-dimethyl-1-piperazinyl-ethoxy-carbonyl.

3. The benzimidazole derivative of claim 2, which is

2-(1-Acetyl-4-piperazinyl)-ethyl 3-(5-(3-furanyl)-1-benzimidazolyl)-benzoate;

1-Methyl-2-pyrrolidylmethyl 3-(5-(3-furanyl)-1-benzimidazolyl)-benzoate;

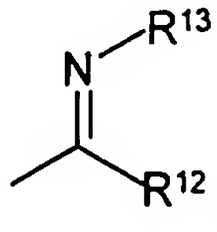
2-(3,5-dimethyl-1-piperazinyl)-ethyl 3-(5-acetylbenzimidazol-1-yl)-benzoate oxime; or

2-(2-pyridyl)-methyl 3-(5-acetylbenzimidazol-1-yl)-benzoate oxime;

or a pharmaceutically acceptable salt thereof.

4. The benzimidazole derivative of claim 1, wherein

R^1 represents a group of the formula $-CO_2R^2$, wherein
R^2 represents alkyl, hydroxy-alkyl, alkoxy-alkyl, thioalkoxy-alkyl, alkyl-$N(alkyl)_2$; or

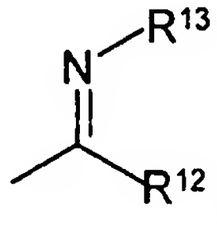
R^1 represents a group of the formula  , wherein

R^{12} represents alkyl, and
R^{13} represents hydroxy, or alkoxy; or

R^1 represents a furanyl group, a pyrazolyl group, an isoxazolyl group, an oxazolyl group, an oxadiazolyl group.

5. The benzimidazole derivative of claim 4, wherein

R^1 represents a group of the formula -COOH, $-CO_2-CH_3$, $-CO_2-C_2H_5$, $-CO_2-CH_2-CH(OH)$, $-CO_2(CH_2)_2OCH_3$, $-CO_2(CH_2)_2SCH_3$, $-CO_2(CH_2)_2SC_2H_5$, or $-CO_2(CH_2)_2N(CH_3)_2$; or

R^1 represents a group of the formula  , wherein

R^{12} represents methyl or ethyl, and
R^{13} represents hydroxy, methoxy or ethoxy; or

R^1 represents a 2- or 3-furanyl group.

6. The benzimidazole derivative of claim 5, which is

2-(3,5-dimethyl-1-piperazinyl)-ethyl 3-(5-acetylbenzimidazol-1-yl)-benzoate oxime; or

2-(2-pyridyl)-methyl 3-(5-acetylbenzimidazol-1-yl)-benzoate oxime;

or a pharmaceutically acceptable salt thereof.

7. The benzimidazole derivative of either of claims 4-5, wherein

R'' represents a group of the formula $-(alkyl)_o$-"Heterocycle", wherein
o is 0 or 1, and

"Heterocycle" represents a furanyl group, a 2H-furanyl group, a 4H-furanyl group, a thienyl group, a pyrrolyl group, a 2H-pyrrolyl (pyrrolinyl) group, a 4H-pyrrolyl (pyrrolidinyl) group, an imidazolyl group, an oxazolyl group, a 2H-oxazolyl (oxazolinyl) group, a 4H-oxazolyl (oxazolidinyl) group, an isoxazolyl group, a 2H-isoxazolyl (isoxazolinyl) group, a 4H-isoxazolyl (isoxazolidinyl) group, an oxadiazolyl group, a 2H-oxadiazolyl (oxadiazolinyl) group, a 4H-oxadiazolyl (oxadiazolidinyl) group, a morpholinyl group, a thiomorpholinyl group, a pyridinyl group, a piperidinyl group, a piperazine group, a homopiperazine group or a tetrazolyl group, which heterocyclic groups may be substituted one or more times with substituents selected from the group consisting of halogen, alkyl, oxo, acyl, alkyl-CO_2H, alkyl-CO_2-alkyl -$(alkyl)_p$-CO_2-aryl, -$(alkyl)_p$-CO_2-aralkyl and alkyl-CO_2-alkyl-$CONR^6R^7$, wherein

R^6 and R^7 independently of each another represent hydrogen or alkyl.

8. The benzimidazole derivative of claim 7, wherein

"Heterocycle" represents a pyrrolidin-1-yl; a piperazin-1-yl; a homopiperazin-1-yl; an imidazol-1-yl; a pyridin-4-yl; a 4H-pyridin-4-yl, in particular a 1,2,5,6-tetrahydro-pyridin-4-yl; a piperidin4-yl; a 2H-isoxazol-3-yl, in particular a 4,5-dihydro-isoxazol-3-yl.

9. The benzimidazole derivative of claim 8, wherein R'' represents

4-ethoxycarbonyl-1-imidazolyl;
4-methoxycarbonyl-1-imidazolyl;
5-((N,N-Diethylcarbamoyl)-methoxycarbonylmethyl)-4,5-dihydroisoxazol-3-yl;
5-((N,N-Dimethylcarbamoyl)-methoxycarbonylmethyl)-4,5-dihydroisoxazol-3-yl;
1-imidazolylmethyl;
4-(1-methyl-5-tetrazolyl)-methyl-1-piperazinyl;
1-ethyl-1,2,5,6-tetrahydropyridin-4-yl;
4-(2-oxazolidinone-5-yl)-methyl)1-piperazinyl;
4-(5-methyloxadiazol-3-yl)-methyl)1-piperazinyl;
4-(3,5-dimethylisoxazol-4-yl)-methyl)1-piperazinyl;
4-(2-oxo-tetrahydrofuran-3-yl)-1-piperazinyl;
4-(2-chloro-5-thienyl)-methyl-1-piperazinyl; or
(1-methyl-2-pyrrolidyl)-methylcarbonyl.

10. The benzimidazole derivative of claim 9, which is

2-Methoxyethyl 1-(3-(4-methoxycarbonyl-1-imidazolyl)-phenyl)-benzimidazole-5-carboxylate;

(N,N-Diethylcarbamoyl)-methyl 2-(3-[3-(5-ethoxycarbonyl-1-benzimidazolyl)-phenyl]-4,5-dihydroxyisoxazol-5-yl)-acetate;

Methyl 1-(3-(1-imidazolylmethyl)-phenyl)-benzimidazole-5-carboxylate;

2-(Methylthio)-ethyl 1-(3-(1-imidazolylmethyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(1-methyl-5-tetrazolyl)methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(1-ethyl-1,2,5,6-tetrahydropyridin-4-yl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(2-oxazolidinone-5-yl)-methyl)1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(5-methyloxadiazol-3-yl)-methyl)1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(3,5-dimethylisoxazol-4-yl)methyl)1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(2-oxo-tetrahydrofuran-3-yl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(2-chloro-5-thienyl)-methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

5-(3-Furanyl)-1-(3-(4-methoxycarbonyl-1-imidazolyl)-phenyl)-benzimidazole;

or

N,N-Diethylcarbamoylmethyl 2-(3-(3-(5-(3-furanyl)-1-benzimidazolyl)-phenyl)-4,5-dihydroisoxazole-5-yl)-acetate;

or a pharmaceutically acceptable salt thereof.

11. The benzimidazole derivative of either of claims 4-5, wherein

R'' represents a group of the formula $-CO_2-(alkyl)_o$-"Heterocycle", wherein

o is 0 or 1, and

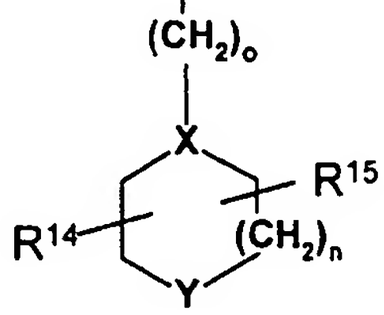
"Heterocycle" represents a pyrrolyl group, a 2H-pyrrolyl (pyrrolinyl) group, a 4H-pyrrolyl (pyrrolidinyl) group, an imidazolyl group, an oxazolyl group, an isoxazolyl group, a 2H-isoxazolyl (isoxazolinyl) group, a 4H-isoxazolyl (isoxazolidinyl) group, an oxadiazolyl group, a pyridyl group, a piperidinyl group, a piperazine group or a homopiperazine group, which heterocyclic groups may be substituted

one or more times with substituents selected from the group consisting of alkyl, acyl, alkyl-CO_2H, alkyl-CO_2-alkyl and alkyl-CO_2-alkyl-$CONR^6R^7$, wherein

R^6 and R^7 independently of each another represent hydrogen or alkyl.

12. The benzimidazole derivative of either of claims 4-5, wherein

R'' represents a group of the formula



in which formula

o is 0 or 1,

n is 0, 1 or 2,

X represents N or CH,

Y represents O, NR^{11} or CHR^{11},

wherein R^{11} represents hydrogen, alkyl, hydroxy-alkyl, alkoxy-alkyl, carboxyl or acyl, or a group of the formula -$(alkyl)_p$-CN, -$(alkyl)_p$-aryl, -$(alkyl)_p$-O-aryl, -$(alkyl)_p$-O-aralkyl, -$(alkyl)_p$-"Heterocycle", -$(alkyl)_p$-CO_2-"Heterocycle" or -$(alkyl\text{-}CO_2)_s$-$(alkyl)_t$-COR^5,

wherein

p, s and t independently of each another is 0 or 1,

"Heterocycle" represents a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halogen, alkyl, hydroxy, oxo, cyano, hydroxy-alkyl, alkoxy-alkyl, carboxyl and acyl,

R^5 represents hydroxy, alkoxy, hydroxy-alkoxy, alkoxy-alkoxy, thioalkoxy-alkoxy, aryl or aralkyl, or a group of the formula -NR^6R^7 or -O-alkyl-NR^6R^7, in which formulas

R^6 and R^7 independently of each another represents hydrogen, alkyl, cycloalkyl or a mono- or polycyclic heterocyclic group, which heterocyclic group is optionally

substituted one or more times with substituents selected from the group consisting of alkyl, and acyl, or

R^6 and R^7 together with the nitrogen to which they are attached form a mono- or polycyclic heterocyclic group, which heterocyclic group may be substituted one or more times with substituents selected from the group consisting of alkyl and acyl, and

R^{14} and R^{15} independently of each another represent hydrogen, alkyl, hydroxy-alkyl, alkoxy-alkyl, carboxyl or acyl; or

R'' represents a group of the formula $-CO_2R^8$, wherein

R^8 represents alkyl-NR^9R^{10}, wherein

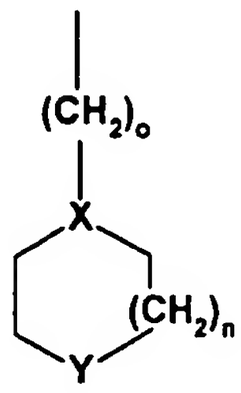
R^9 and R^{10} together with the nitrogen to which they are attached form a pyrrolidine or a piperazine group, which group may be substituted one or more times with substituents selected from the group consisting of alkyl and acyl.

13. The compound according to claim 12, wherein R'' represents
4-methoxycarbonyl-methyl-3,5-dimethyl-1-piperazinyl;
4-ethoxycarbonyl-methyl-3,5-dimethyl-1-piperazinyl;
4-methyl-3,5-dimethyl-1-piperazinyl;
4-ethyl-3,5-dimethyl-1-piperazinyl; or
3,5-dimethyl-1-piperazinyl.

14. The compound according to claim 12, which compound is
2-Methoxyethyl 1-(3-(4-ethoxycarbonylmethyl-3,5-dimethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;
2-Methyl 1-(3-(4-ethoxycarbonylmethyl-3,5-dimethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(4-ethyl-3,5-dimethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(3,5-dimethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate; or
2-(3,5-dimethyl-1-piperazinyl)-ethyl 3-(5-acetylbenzimidazol-1-yl)-benzoate oxime;
or a pharmaceutically acceptable salt thereof.

15. The benzimidazole derivative of claim 12, wherein

R'' represents a group of the formula



in which formula

o is 0 or 1,

n is 0, 1 or 2,

X represents N or CH, and

Y represents NR^{11} or CHR^{11}, wherein

R^{11} represents hydrogen, alkyl, hydroxy-alkyl, carboxy, acyl, or a group of the formula $-(alkyl)_p-CN$, $-(alkyl)_p-aryl$, $-(alkyl)_p-O-aryl$, $-(alkyl)_p-O-aralkyl$, $-(alkyl)_t-COR^5$ or $-(alkyl)_t-R^5$,

wherein

p and t independently of each another is 0 or 1, and

R^5 represents hydroxy, alkoxy, NH_2, NH(alkyl) or $N(alkyl)_2$.

16. The benzimidazole derivative of claim 15, wherein R'' represents

4-(methoxy-carbonyl)-1-piperazinylmethyl;

4-(ethoxy-carbonyl)-1-piperazinylmethyl;

4-(methoxy-carbonyl-methyl)-1-piperazinyl;

4-(ethoxy-carbonyl-methyl)-1-piperazinyl;

4-(methoxy-carbonyl-methyl)-1-piperazinylmethyl;

4-(ethoxy-carbonyl-methyl)-1-piperazinylmethyl;

1-piperazinyl;

1-piperazinyl-methyl;

4-acetyl-1-piperazinyl;

4-methyl-1-piperazinyl;

4-ethyl-1-piperazinyl;

1-methyl-4-piperidinyl;

1-acetyl-4-piperidinyl;

1-methyl-4-piperidyl;

1-acetyl-4-piperidyl;

4-*tert*-butoxycarbonylmethyl-1-piperazinyl;

4-isopropoxycarbonylmethyl-1-piperazinyl;

4-carboxymethyl-1-piperazinyl;

4-benzyl-1-piperazinyl;
4-cyanomethyl-1-piperazinyl;
4-benzyloxy-ethyl-1-piperazinyl;
4-ethyl-1-homopiperazinyl;
4-(2-hydroxy-ethyl)-1-piperazinyl;
4-carbamoylmethyl-1-piperazinyl;
4-dimethylcarbamoylmethyl-1-piperazinyl; or
4-diethylcarbamoylmethyl-1-piperazinyl.

17. The compound according to claim 15, which compound is

2-Methoxyethyl 1-(3-(4-(ethoxycarbonyl)-1-piperazinylmethyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(etoxycarbonylmethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-carboxymethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Metoxyethyl 1-(3-(4-acetyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(1-methyl-4-piperidyl)phenyl)benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(1-acetyl-4-piperidyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-*t*-butoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-*i*-propoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-[4-(3-(5-Methoxycarbonylbenzimidazol-1-yl)-phenyl)-1-piperazinyl]-acetic acid;

2-(Methylthio)-ethyl 1-(3-(4-methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-(N,N-dimethylamino)-ethyl 1-(3-(1-carboxymethyl-4-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-benzyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

Methyl 1-(3-(4-cyanomethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-cyanomethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

Methyl 1-(3-(4-benzyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-benzyloxyethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-ethyl-1-homopiperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methyl 1-(3-(4-ethyl-1-homopiperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-ethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-(2-hydroxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

Methyl 1-(3-(1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-methoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-ethoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-diethylcarbamoylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-methoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-carbamoylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-carbamoylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-diethylcarbamoylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-carboxymethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate;

5-(3-Furanyl)-1-(3-((4-ethoxycarbonyl-1-piperazinyl)-methyl)-phenyl)-benzimidazole;

5-(3-Furanyl)-1-(3-(1-(ethoxycarbonylmethyl)-4-piperazinyl)-phenyl)-benzimidazole;

5-(3-Furanyl)-1-(3-(4-t-butoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole;

5-(3-Furanyl)-1-(3-(1-ethoxycarbonylmethyl-4-piperazinylmethyl)-phenyl)-benzimidazole;

5-(3-Furanyl)-1-(3-(1-ethoxycarbonylmethyl-4-piperidyl)-phenyl)-benzimidazole;

5-(3-Furanyl)-1-(3-(4-ethoxycarbonylpiperid-1-ylmethyl)-phenyl)-benzimidazole; or

5-(3-Furanyl)-1-(3-(1-ethoxycarbonyl-4-piperazinyl)-phenyl)-benzimidazole; or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition containing a therapeutically effective amount of a benzimidazole derivative according to any of claims 1-17, or a pharmaceutically acceptable addition salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

19. The use of a benzimidazole derivative according to any of claims 1-17 for the manufacture of a medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of the GABA receptor complex.

20. The use according to claim 19, wherein the medicament is for inducing anaesthesia, pre-anaesthesia, muscle relaxation, or sedation, or for treatment, prevention or alleviation of fewer cramps or status epilepticus.

21. A method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of the GABA receptor complex, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a benzimidazole derivative according to any of claims 1-17.

22. The method according to claim 21, for the induction or maintenance of anaesthesia or pre-anaesthesia, muscle relaxation or sedation, or for the treatment, prevention or alleviation of fewer cramps or status epilepticus.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00333

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 235/06, C07D 401/10, C07D 403/10, C07D 405/14, C07D 409/02, C07D 413/14, A61K 31/4184, A61K 31/496, A61P 21/00, A61P23/00, A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9817651 A1 (NEUROSEARCH A/S), 30 April 1998 (30.04.98), the claims and examples ---	1-22
X	WO 9633194 A1 (NEUROSEARCH A/S ET AL), 24 October 1996 (24.10.96), the claims and examples ---	1-22
X	WO 9919323 A1 (NEUROSEARCH A/S ET AL), 22 April 1999 (22.04.99), the claims and examples ---	1-22
X	WO 9633191 A1 (NEUROSEARCH A/S ET AL), 24 October 1996 (24.10.96), the claims and examples ---	1-22

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" erlier document but published on or after the international filing date

"L" document which may throw douhts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
25 October 2000

Date of mailing of the international search report
30. 11. 2000

Name and mailing address of the International Searching Authority
European Patent Office P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel(+31-70)340-2040, Tx 31 651 epo nl,
Fax(+31-70)340-3016

Authorized officer
SOLVEIG GUSTAVSSON/ELY
Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00333

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0616807 A1 (MEIJI SEIKA KAISHA LTD.), 28 Sept 1994 (28.09.94), the claims and examples ---	1-22
X	WO 9633192 A1 (NEUROSEARCH A/S ET AL), 24 October 1996 (24.10.96), the claims and examples ---	1-22
X	US 5554632 A (LENE TEUBER ET AL), 10 Sept 1996 (10.09.96), the claims and examples ---	1-22
X	US 5554630 A (LENE TEUBER ET AL), 10 Sept 1996 (10.09.96), the claims and examples ---	1-22
X	WO 9834923 A1 (MERCK SHARP & DOHME LIMITED), 13 August 1998 (13.08.98), the claims --- --------	1-22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00333

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 21-22
because they relate to subject matter not required to be searched by this Authority, namely:

See extra sheet.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00333

Claims 21-22 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compound(s)/composition(s).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/DK 00/00333

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9817651 A1	30/04/98	AU 4616197 A	15/05/98
		CN 1234025 A	03/11/99
		CZ 9901272 A	15/09/99
		EP 0934281 A	11/08/99
WO 9633194 A1	24/10/96	AT 194836 T	15/08/00
		AU 695957 B	27/08/98
		AU 699623 B	10/12/98
		AU 5501496 A	07/11/96
		AU 5689196 A	07/11/96
		AU 5690696 A	07/11/96
		BR 9608048 A	30/11/99
		BR 9608056 A	30/11/99
		CA 2217601 A	24/10/96
		CA 2218493 A	24/10/96
		CA 2218552 A	24/10/96
		CN 1182425 A	20/05/98
		CN 1182426 A	20/05/98
		CN 1182427 A	20/05/98
		CZ 9703291 A	18/03/98
		CZ 9703292 A	18/03/98
		DE 69609413 D	00/00/00
		EP 0821682 A,B	04/02/98
		EP 0821683 A	04/02/98
		EP 0821684 A	04/02/98
		HU 9801692 A	29/03/99
		HU 9802272 A	28/09/99
		JP 3040485 B	15/05/00
		JP 11501320 T	02/02/99
		JP 11501321 T	02/02/99
		JP 11511734 T	12/10/99
		NO 974843 A	15/12/97
		NO 974844 A	16/12/97
		NZ 307521 A	29/04/99
		NZ 307532 A	29/03/99
		PL 322892 A	02/03/98
		PL 322944 A	02/03/98
		RU 2135493 C	27/08/99
		RU 2136676 C	10/09/99
		SK 139997 A	06/05/98
		SK 140697 A	06/05/98
		US 5902813 A	11/05/99
		US 5922724 A	13/07/99
		US 5922725 A	13/07/99
		WO 9633191 A	24/10/96
		WO 9633192 A	24/10/96
WO 9919323 A1	22/04/99	AU 9433298 A	03/05/99
		EP 1023286 A	02/08/00
		ZA 9809238 A	17/05/99

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/DK 00/00333

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9633191 A1	24/10/96	AT 194836 T	15/08/00
		AU 695957 B	27/08/98
		AU 699623 B	10/12/98
		AU 5501496 A	07/11/96
		AU 5689196 A	07/11/96
		AU 5690696 A	07/11/96
		BR 9608048 A	30/11/99
		BR 9608056 A	30/11/99
		CA 2217601 A	24/10/96
		CA 2218493 A	24/10/96
		CA 2218552 A	24/10/96
		CN 1182425 A	20/05/98
		CN 1182426 A	20/05/98
		CN 1182427 A	20/05/98
		CZ 9703291 A	18/03/98
		CZ 9703292 A	18/03/98
		DE 69609413 D	00/00/00
		EP 0821682 A,B	04/02/98
		EP 0821683 A	04/02/98
		EP 0821684 A	04/02/98
		HU 9801692 A	29/03/99
		HU 9802272 A	28/09/99
		JP 3040485 B	15/05/00
		JP 11501320 T	02/02/99
		JP 11501321 T	02/02/99
		JP 11511734 T	12/10/99
		NO 974843 A	15/12/97
		NO 974844 A	16/12/97
		NZ 307521 A	29/04/99
		NZ 307532 A	29/03/99
		PL 322892 A	02/03/98
		PL 322944 A	02/03/98
		RU 2135493 C	27/08/99
		RU 2136676 C	10/09/99
		SK 139997 A	06/05/98
		SK 140697 A	06/05/98
		US 5902813 A	11/05/99
		US 5922724 A	13/07/99
		US 5922725 A	13/07/99
		WO 9633192 A	24/10/96
		WO 9633194 A	24/10/96

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/DK 00/00333

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5554632 A	10/09/96	AT 168007 T	15/07/98
		AU 675484 B	06/02/97
		AU 5752194 A	29/09/94
		CA 2119511 A	25/09/94
		CN 1099391 A	01/03/95
		DE 69411424 D,T	28/01/99
		DK 33793 D	00/00/00
		EP 0616807 A,B	28/09/94
		ES 2119124 T	01/10/98
		FI 941378 A	25/09/94
		JP 7002838 A	06/01/95
		NO 306464 B	08/11/99
		NO 941052 A	26/09/94
		NZ 260050 A	26/01/96
		US 5554630 A	10/09/96
		ZA 9402079 A	24/10/94
		DK 105593 D	00/00/00
US 5554630 A	10/09/96	AT 168007 T	15/07/98
		AU 675484 B	06/02/97
		AU 5752194 A	29/09/94
		CA 2119511 A	25/09/94
		CN 1099391 A	01/03/95
		DE 69411424 D,T	28/01/99
		DK 33793 D	00/00/00
		EP 0616807 A,B	28/09/94
		ES 2119124 T	01/10/98
		FI 941378 A	25/09/94
		JP 7002838 A	06/01/95
		NO 306464 B	08/11/99
		NO 941052 A	26/09/94
		NZ 260050 A	26/01/96
		US 5554632 A	10/09/96
		ZA 9402079 A	24/10/94
		DK 105593 D	00/00/00
WO 9834923 A1	13/08/98	AU 5874498 A	26/08/98
		EP 0968191 A	05/01/00
		EP 1015904 A	05/07/00
		GB 9702524 D	00/00/00
		US 6071909 A	06/06/00
		WO 9914615 A	25/03/99

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/DK 00/00333

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0616807 A1	28/09/94	AT 168007 T	15/07/98
		AU 675484 B	06/02/97
		AU 5752194 A	29/09/94
		CA 2119511 A	25/09/94
		CN 1099391 A	01/03/95
		DE 69411424 D,T	28/01/99
		DK 33793 D	00/00/00
		ES 2119124 T	01/10/98
		FI 941378 A	25/09/94
		JP 7002838 A	06/01/95
		NO 306464 B	08/11/99
		NO 941052 A	26/09/94
		NZ 260050 A	26/01/96
		US 5554630 A	10/09/96
		US 5554632 A	10/09/96
		ZA 9402079 A	24/10/94
		DK 105593 D	00/00/00